The Journal of
CLINICAL
ENDOCRINOLOGY

VOLUME 4 JANUARY, 1944 NUMBER 1
Copyright 1944 by the Association for the Study of Internal Secretions

The Action of Thiouracil upon the Thyroid Gland in Graves' Disease[1]

RULON W. RAWSON,[2] M.D.,
R. D. EVANS, Ph.D.,
J. H. MEANS, M.D.,
W. C. PEACOCK, Ph.D.,
J. LERMAN, M.D., AND
R. E. CORTELL, Ph.D.

From the Thyroid Clinic of the Massachusetts General Hospital and the Radio-Activity Center of the Department of Physics, Massachusetts Institute of Technology, Boston, Massachusetts.

THE demonstration by the Mackenzies (1) and by Astwood and his collaborators (2, 3) that thiourea and related compounds affect the thyroid gland in a striking and peculiar manner placed in the hands of thyroidologists both a new tool for studying thyroid physiology and a therapeutic agent of interesting potentialities.

Prior to the reports of the investigators just mentioned, our interest in goitrogenous agents had been aroused by the finding of patients made goiterous by the use of thiocyanate for the treatment of hypertension (4). When the thioureas appeared on the scene, therefore, we decided at once to obtain personal experience in the use of such an agent in cases of Graves' disease. We selected thiouracil, the member of this group advocated by Astwood (5) as most suitable for this purpose.

Three questions particularly interested us. First, what is the action of thiouracil upon the thyroid gland in Graves' disease? Second, what is its value as a preparation for thyroidectomy in Graves' disease? And third, what is its value as a treatment *per se* in Graves' disease? Inasmuch as others (5, 6) were working on the last question we decided to concentrate on the first and second. The action upon the gland is the subject of the present paper. Thiouracil as

[1] Aided by grants from the Josiah Macy, Jr. Foundation and the John and Mary R. Markle Foundation. We are grateful to Lederle Laboratories, Incorporated, for supplying the thiouracil used in these studies.

[2] Henry P. Walcott Fellow in Clinical Medicine, Harvard University.

a preparation for thyroidectomy is the subject of a paper which will be published elsewhere (7).

Before we commenced our studies Dr. Astwood had very kindly shown us his experimental work and early clinical results. In animals he had demonstrated that many compounds related to thiourea acted upon the thyroid to make it hyperplastic and at the same time induced a state of hypothyroidism in the animal. To this extent the action of these compounds resembled that of thiocyanate (4). In patients with Graves' disease also, Astwood had shown that the exhibition of thiouracil caused a fall in metabolic rate and amelioration of symptoms, which are maintained so long as the drug is continued (5).

We determined to administer thiouracil in classic Graves' disease both alone, and in conjunction with iodine, and then to have the patients thyroidectomized if their condition seemed to warrant it. We proposed to observe the effects of the drug both in the patient and in his gland removed at operation. In five cases we obtained biopsies of the thyroid before thiouracil was started to compare with the tissue removed at operation after thiouracilization.

The first of our thyroidectomies in a patient with Graves' disease—Mr. M. (Lab. No. 23895)—prepared only with thiouracil, not receiving any iodine, was performed on June 24, 1943. It was with considerable trepidation that we approached this operation. The patient had made a symptomatic and metabolic improvement on thiouracil quite as good as would have been expected on iodine. Nevertheless we were apprehensive about what would happen at operation. To our great relief all went very well and the patient made an uneventful convalescence from the operation.

We now have a total of 19 cases of Graves' disease in which thyroidectomy was performed with no preparation but thiouracil. We have three patients who are being followed on this drug as a treatment *per se*, and we have observations on 3 patients who received both iodine and thiouracil simultaneously.

In the present paper we will present the evidence on the nature of the drug action furnished by the 19 cases in which thyroidectomy was done after preparation with thiouracil alone. The case histories of these patients and the description of the operative and postoperative courses will be given in another paper (7). Also the precise dosage of thiouracil administered will be shown in the individual charts in that paper. The dosage used was that advocated by Astwood; namely, 0.6 grams per day by mouth to start, with a reduction sometimes to 0.4 grams per day after the basal metabolic rate had dropped half-way to normal.

Effect on Basal Metabolic Rate

Basal metabolic rate may be considered an expression of the total effect of thyroid hormone upon its end-organs—the cells of the body. Two primary factors are concerned—the actual rate of output of hormones by the gland and the capability of the end-organs to be stimulated thereby. A fall in metabolic rate could be due to diminished hormone output, as in myxedema, or it could be due to end-organ insensitivity. Whether a state of end-organ insensitivity or hyposensitivity actually occurs remains to be proven.

The metabolic responses to thiouracil in our first 15 cases of Graves' disease, virgin with respect to iodine, together with their composite, are shown in figure 1. In this figure also is shown the iodine response composite previously obtained in this clinic by Means and Lerman (8). The slopes of the two curves are quite similar.

In patients who had received iodine treatment prior to thiouracil the response was delayed.

Astwood (5) has advanced the theory that thiouracil acts by preventing the completion of physiologically active hormone and does not affect preformed hormone.

Means and Lerman concluded (8) that the iodine-response curve is, in fact, a thyroxin-decay curve; that is to say, it is the result of shutting off the delivery of new thyroid hormone from gland to body[3] and the using up of what hormone was in circulation when the administration of iodine was begun.

---

[3] For the argument on which this conclusion is based, please see the original communication (8).

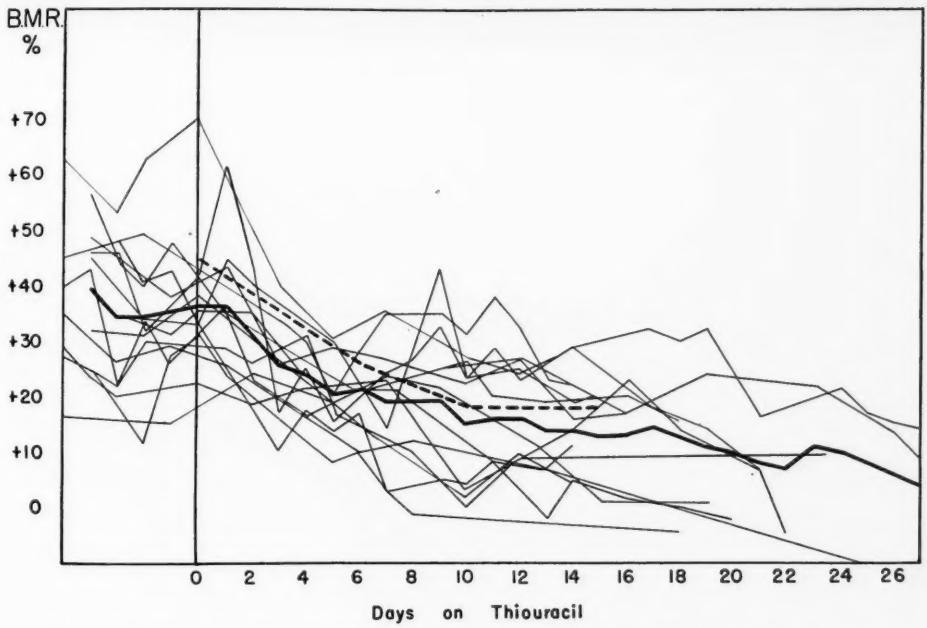


FIG. 1. Basal metabolic response to thiouracil in Graves' disease. The heavy solid line is the composite. The broken line is the iodine-response composite of Means and Lerman (8).

Since the thiouracil curve is the same shape as the iodine-response curve, it too may be regarded as a thyroxin-decay curve. In those thyrotoxic patients who have had no iodine, there is, presumably, little or no stored hormone. When thiouracil is exhibited, new formation of hormone is stopped and the curve represents the consumption of what hormone was in circulation when administration of the drug was begun.

However, in patients who have had iodine prior to thiouracil, there probably is considerable stored hormone, which continues to come out after administration of the drug is started, even though new hormone does not. This may explain the delayed action.

Histologic Effects

The histologic appearance of the thiouracil-treated thyroids was of interest. In general all of the thyroids showed moderate hypertrophy to marked hyperplasia. The colloid was markedly diminished to absent. In one instance, F. P., Lab. No. 24282, the normal acinar structure was almost completely replaced by cellular elements. In a few parts of the gland the acinar structure was replaced by columns of acinar epithelial cells (fig. 2).

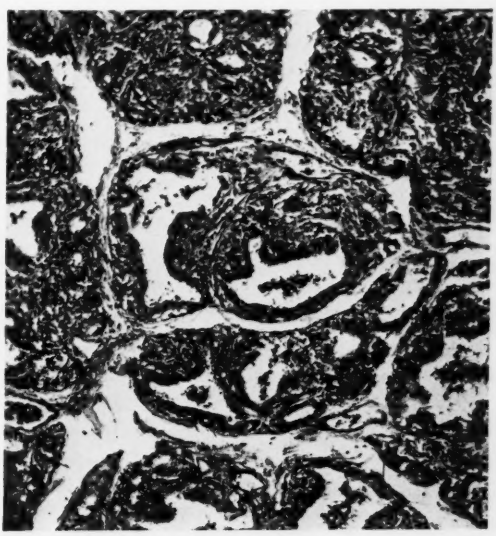


FIG. 2. Photomicrograph (×100) of thyroid obtained at operation after thiouracil, patient F. P., no. 24282, showing marked hyperplasia and replacement of acinar structure by cellular elements.

TABLE I. THYROID CELL HEIGHTS BEFORE AND AFTER THIOURACIL IN PATIENTS WITH GRAVES' DISEASE

Patient	Lab. No.	Age	Sex	MACH[1] of biopsy in micra	Mean acinar cell height of thyroid removed at operation in micra					
					Number of sample					Average
					1	2	3	4	5	
B. B.	Private Patient of Drs. R. R. Linton & B. L. Decker	53	F	12.04	12.9	13.2	13.0	13.2	12.9	13.0
R. R.	24218	18	M	13.2	15.2	15.0	15.0	15.3	15.1	15.1
W. L.	24260	18	M	9.2	10.2	10.2	10.0	10.0		10.1
M. M.	24227	40	M	10.0	10.5	10.3	10.3	10.8	11.3	10.6
F. D.	24336	28	F	11.0	14.3	15.3	15.6	15.4		15.2

[1] Mean Acinar Cell Height.

In view of the experimental observations on the marked thyroid hyperplasia in rats maintained on thiouracil (1, 2, 3) and in view of the histologic picture of the thyroids removed from patients treated with this agent a natural question presents itself. Does the administration of thiouracil or other goitrogens increase the thyroid hypertrophy and hyperplasia of Graves' disease? To answer this question biopsies were taken from the thyroids of five patients before thiouracil treatment was begun. The histologic picture of the biopsy specimen was compared with that of histologic preparations from at least four different areas of the glands removed at operation. These preparations were examined under oil immersion and the height of one representative acinar cell from each of one hundred successive acini was determined in each preparation. In three cases, though there was some increase in the mean acinar cell heights of the post-thiouracil-treatment specimens of the thyroids as compared

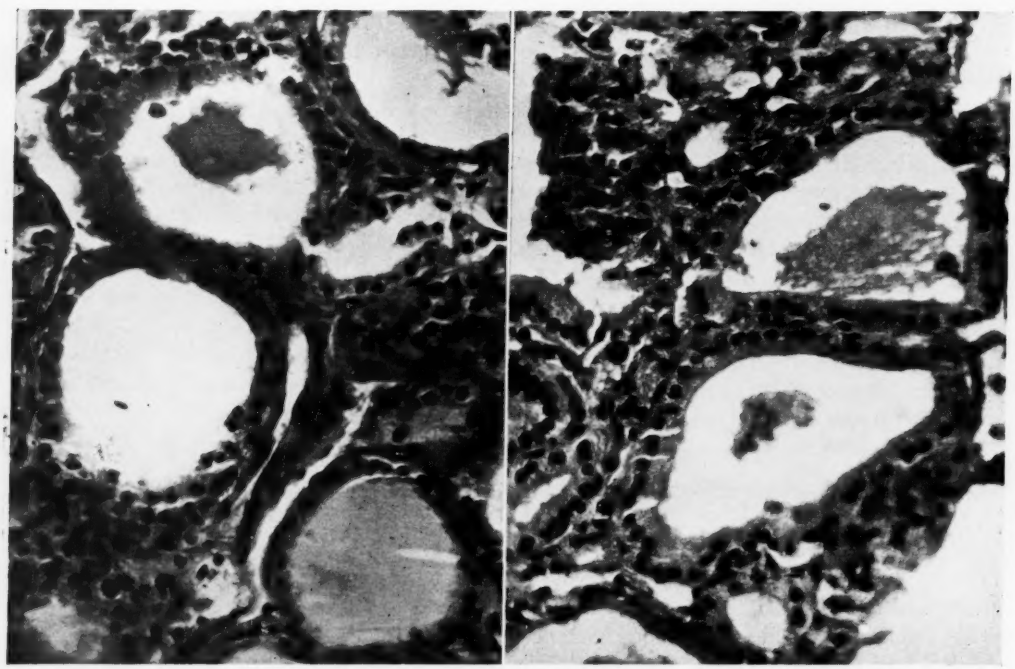


FIG. 3. Photomicrographs (×340) of thyroid of patient F. D., no. 24336: on the left, at biopsy before thiouracil; on the right, at operation after thiouracil. Note the increase in thyroid hypertrophy following exhibition of this drug.

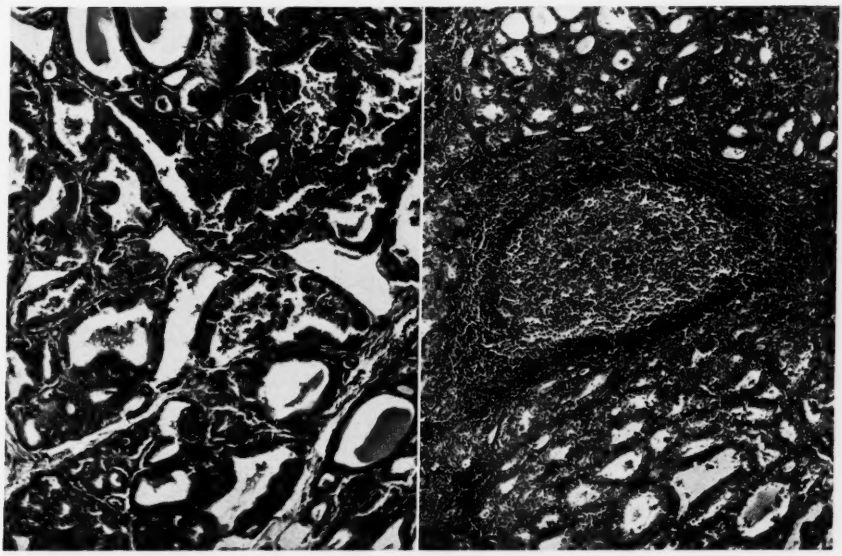


FIG. 4. Photomicrograph (×85) of the thyroid of B. B. (private patient): on the left, at biopsy before thiouracil; on the right, at operation after thiouracil. Note the lymphoid hyperplasia in the post-thiouracil specimen.

to the mean acinar cell heights of the biopsy specimens, the increase was not enough to be of significance. The mean acinar cell height of the post-thiouracil-treatment specimens of two patients were significantly increased over the mean acinar cell heights of the biopsy specimens, *i.e.*, increases of 4.2 and 2.0 micra (table I and fig. 3).

The biopsy specimen removed from one patient showed only thyroid hypertrophy and hyperplasia. Tissues examined at operation after thiouracil treatment also showed hyperplasia of lymphoid tissue. Indeed in several areas the normal acinar picture of thyroid was almost completely replaced by lymph follicles (fig. 4).

In comparing the histologic picture with the clinical response and BMR response of the patient to thiouracil treatment we observed that the patients who had made the most prompt response to treatment with this drug were those whose thyroids histologically demonstrated the most marked hyperplasia and the least colloid in the follicles (table II). E. K., Lab. No. 24085, had a fall in basal metabolic rate from +38 to +2 in 10 days. Her thyroid showed extreme hyperplasia and no colloid (fig. 5). F. D., Lab. No. 24336, had a fall in BMR from +60 to +7 in 20 days. A biopsy specimen of her thyroid as well as sections of the removed thyroid after thiouracil treatment showed marked thyroid hypertrophy and loss of colloid (fig. 3). W. L., Lab. No. 24260, who had taken iodine until the time of his admission to the hospital, made a very slow response to the drug. His basal metabolic rate fell from +40 to +12. His thyroid showed involution and even hyperinvolution in some areas (fig. 6). M. B., Lab. No. 24273, a 49-year-old woman who had had a goiter for 15 years and had had symptoms of thyrotoxicosis for 5 months had a large firm goiter which at operation weighed 130 grams. Her response to thiouracil treatment was slow. Her basal-metabolic-rate level fell from +20 to +7 in 20 days. Her thyroid showed moderate hypertrophy and evidence of old involution (fig. 7).

Effect on Collection of Labelled Iodine by Thyroid

The uptake of radioactive iodine (half period = 8 days) was studied in patients treated with thiouracil. Ten patients who had been prepared for thyroidectomy with thiouracil were each given a tracer dose of radioactive iodine (150

TABLE II. COMPARISON BETWEEN BMR RESPONSE OF PATIENTS WITH GRAVES' DISEASE TO THIOURACIL AND HISTOLOGIC PICTURE IN THE THYROID.

Patient	Laboratory no.	Age	Sex	Fall in BMR	In number of days	Degree of thyroid hypertrophy and hyperplasia
M. B.	24033	34	F	+29 to + 7	14	+
A. S.[1]	23905	51	F	+26 to +16	20	++
F. D.	24336	28	F	+60 to + 7	22	++++
R. R.	24218	18	M	+48 to +22	16	++++
J. W.	24168	61	M	+18 to + 1	15	+++
L. A.	24361	42	F	+34 to + 3	12	++++
R. S.	24170	48	F	+40 to +20	15	++
J. S.	24049	30	F	+38 to +17	16	++++
M. M.	24227	40	M	+19 to +11	12	++
E. K.	24085	20	F	+38 to + 2	11	+++++
S. M.	23895	42	M	+40 to + 7	30	+++
W. L.[1]	24260	18	M	+41 to +12	30	+
L. O'B.	24405	30	F	+36 to + 3	10	++++
B. B.	Private Patient of Drs. R. R. Linton & B. L. Decker	53	F	+29 to +12	15	++++
F. P.[2]	24282	21	F	+35 to + 7 to −16	12 30	++++++
M. B.	24273	49	F	+20 to + 7	22	++
B. K.[3]	24323	39	F	+35 to − 8	26	+++++
J. R.	24469	53	F	+44 to + 1	36	++
M. G.	24472	35	F	+29 to − 3	15	++++

[1] Took iodine until admission to hospital.

[2] Developed two dental abscesses which required surgical treatment thus causing delay in operation. Developed picture of myxedema before operation.

[3] Took iodine for 9 months before admission to hospital. While on iodine a hemi-thyroidectomy was done. Iodine then was stopped. Thiouracil was exhibited 15 days later.

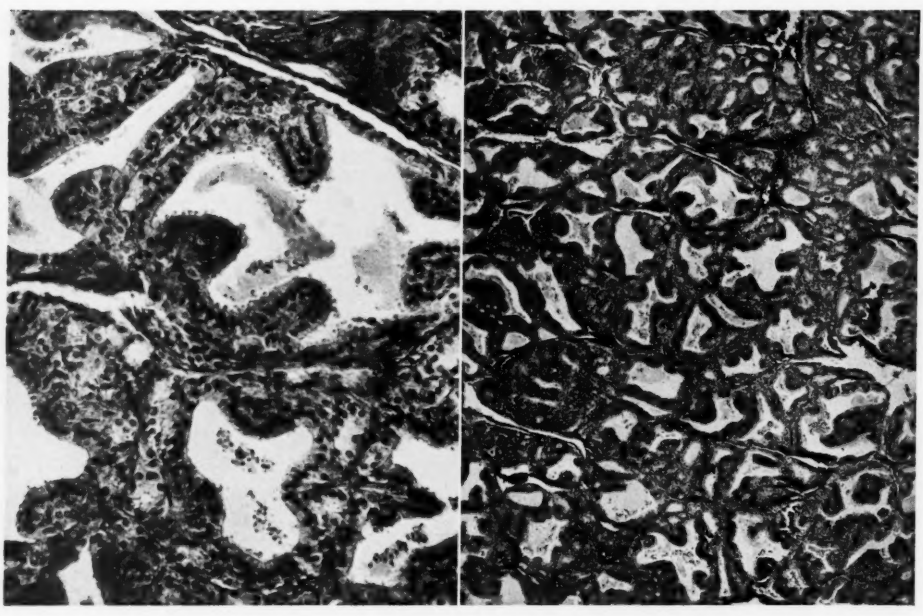


FIG. 5. Photomicrographs of the thyroid of patient E. K., no. 24085, at operation after thiouracil on the left (×170), on the right (×43). Note the marked hyperplasia with papillary infoldings, and scarcity of colloid.

FIG. 6. Photomicrograph (×50) of the thyroid of patient W. L. no. 24260, at operation after thiouracil. Note the involution and minimal hypertrophy. This patient received iodine up to time of admission to hospital.

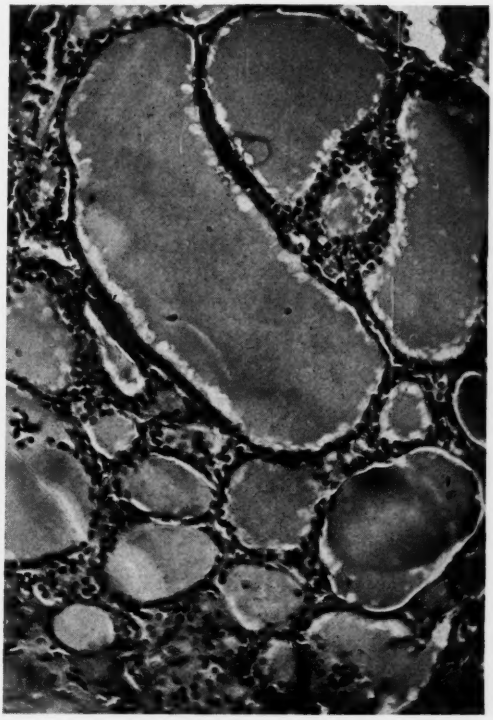


FIG. 7. Photomicrograph (×200) of the thyroid of patient, M. B., no. 24273, at operation after thiouracil. Note again involution. This patient had had a goiter for 15 years; it only recently had become toxic.

gamma of iodine as sodium iodide) 48 to 24 hours before operation. All of the urine excreted from the time of radioactive-iodine administration to the time of operation was collected in 24-hour amounts. The per cent of administered radioactivity contained in the urine then was determined. Samples of thyroid tissue then were weighed and placed in 3 cc. two per cent sodium hydroxide for digestion of the tissue. The radioactivity contained in each sample of thyroid tissue then was determined and calculated on the basis of the weight of the removed thyroid gland. With one exception all of the patients excreted in the first 24 hours more than 55% of the administered tracer iodine. One patient excreted only 27%. Normal people excrete about 80%. The amount of radioactivity demonstrated in the thyroid tissue following its removal was consistent with the amount recovered in the urine (table III).

Tracer doses of radioactive iodine were given to one patient five days before starting the thiouracil and also 1 day, 7 days, and 12 days after starting treatment with thiouracil. In the five-day period after administration of the first dose of radioactive iodine, given before any treatment was started, only 13% of the administered iodine was excreted. Of the tracer iodine administered 24 hours after starting thiouracil treatment, 46% was excreted within 24 hours and 120% of the amount administered, which probably included some of the first-administered iodine, was excreted in the six-day period. In the five-day period following administration of the tracer iodine on the 7th day of thiouracil treatment, 51% of one tracer dose was excreted. Of a tracer dose, 110% was excreted in the five-day period following administration of 150 gamma of radioactive iodine on the 12th day of treatment with thiouracil (fig. 8).

TABLE III. COLLECTION AND EXCRETION OF LABELLED IODINE BY PATIENTS WITH GRAVES' DISEASE TREATED WITH THIOURACIL.

Patient	Lab. No.	Age	Sex	Per cent of administered radioactive iodine demonstrated in urine		Per cent of administered radioactive iodine demonstrated in total removed thyroid (measurements based on activity demonstrated in digests of weighed samples and calculated on basis of removed thyroid weights)					
				1st 24-hour period	2nd 24-hour period	Number of sample					
						1	2	3	4	5	6
S. M.	23895	42	M	87%		36					
M. B.	24033	34	F	27		63	44	77			
E. K.	24085	20	F	57		36	53	52	58	33	
J. S.	24049	30	F	65	17	10	9	6	7	4	
J. W.	24168	61	M	82		24	3	5	3	3	
M. B.	24273	49	F	79		21	13	16	15	16	
B. B.	Private Patient of Drs. R. R. Linton & B. L. Decker	53	F	88		6	6	10	23		
L. A.	24361	42	F	60	9	17	10	21	16	17	24
F. P.[1]	24282	21	F	a 72	25						
F. P.[1]	24282	21	F	b 93		15	13	0	0		
B. K.	24323	39	F	66	5	12	14	26			

[1] Developed fever due to dental abscesses evening after receiving first tracer dose of radioactive iodine. Operation was postponed for 18 days. Second tracer iodine given 24 hours before operation.

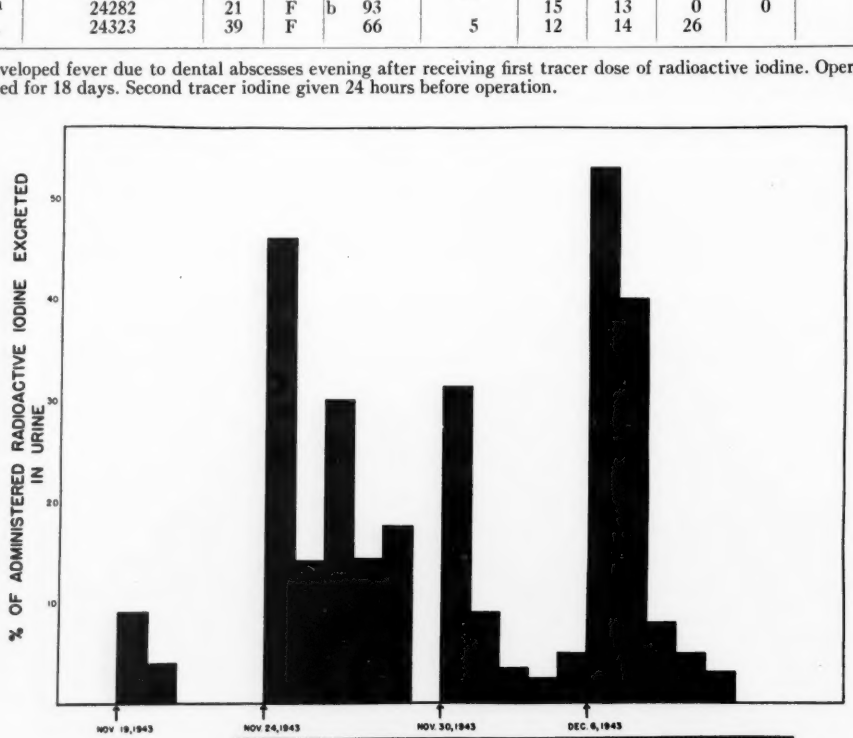


FIG. 8. Excretion of radioactive iodine per 24-hours before and at various stages during thiouracilization in patient L. O'B. no. 24405.

Effect of Treatment with Thiouracil on Physiologic Activity of Subjects' own Thyroglobulin

In order to throw further light on the mode of action of thiouracil, the glands removed from patients with Graves' disease treated with thiouracil were assayed for calorigenic activity. Glands removed surgically were ground and extracted with dilute alkali. The clear supernatant fluid was acidified with

dilute acetic acid to a pH of 5.0 at which point thyroglobulin precipitates. The material obtained was purified by repeated washing and one reprecipitation. The percentage of total iodine in this thyroglobulin was lower than that found in thyroglobulin derived from untreated hyperplastic glands of Graves' disease.

The thyroglobulin obtained from the gland of a patient who had been on thiouracil for five weeks before operation[4] (S. M., No. 23895) was fed daily to a patient with myxedema (G. L., No. 24181) for 12 days. The dosage in terms of nitrogen was the same as the standard amount of ordinary thyroglobulin used in similar assays, namely 0.25 gm., containing 0.5 mg. of iodine. Since thyroglobulin derived from this thiouracil-treated gland contained only 0.06% iodine, the daily dose of the test material contained 0.13 mg. of iodine—an amount equivalent to 1 grain of desiccated thyroid. To this dosage of material there was no clinical or metabolic response.

Another myxedema patient (A.S., No. 24242) received thyroglobulin derived from the goiters of two patients who had received thiouracil for about 15 days each. Here also the daily dose of thyroid protein was 0.22 gm. Since the iodine content of the test preparation was 0.1%, the daily dose contained about 0.22 mg. of iodine, equivalent to about 0.1 gm. ($1\frac{1}{2}$ grains) desiccated thyroid. On this dosage the patient made no clinical response. The BMR fluctuated a good deal because of infection. The serum cholesterol actually rose from 250 mg. to 335 mg. per 100 cc.

A third patient with myxedema was treated for 13 days with thyroglobulin derived from two separate lots of glands. The first lot contained glands from three patients treated with thiouracil, all of which showed a high degree of hyperplasia. After daily administration of 1 gm. of thyroglobulin for 7 days there was no response; but the iodine content of this batch of material was very low (0.009%). The second lot, when fed in dosage of 1.1 gm. protein for 6 days, produced a moderate metabolic response. However, the iodine content of this material was rather high—0.11%—so that the daily dose contained 1.2 mg. of iodine, equivalent to 0.6 gm. (9 grains) of desiccated thyroid. For this amount of material, the response was substandard.

It was discovered later that one of the glands still contained a good deal of colloid tissue. It is possible, therefore, that the response obtained may have been due to the preformed normal thyroglobulin which this batch contained.

From these observations it appears first that thiouracil deprives thyroglobulin, partially at least, of its iodine moiety. With this loss, as would be expected from previous work, there is a corresponding loss in physiologic activity.

DISCUSSION

It is clear from the observations made on this group of patients that thiouracil when administered to patients with Graves' disease will effect a fall in the basal metabolic rate. This fall in metabolic rate is associated with an alleviation of the symptoms of thyrotoxicosis.

Though most of the patients were observed to make metabolic-rate responses as good as those observed in iodine-treated patients, in most instances the histologic picture of the thyroids removed at operation was that of marked hypertrophy and hyperplasia. This histologic picture is what one would expect to observe on the basis of the hyperplastic changes seen in the thyroid glands of rats treated with thiouracil. In five instances the histologic specimens taken at biopsy before thiouracil administration were compared with preparations from several parts of the thyroids removed at operation after thiouracil. In the post-treatment specimens taken from two patients there was a significant increase in the degree of hypertrophy. In a third case there was very definite hyperplasia of lymphoid tissue in the specimen obtained at operation. This was not seen in the specimen obtained at biopsy before treatment with thiouracil. In most instances there was also an apparent increase in vascularity at operation.

It is of practical and of theoretical importance that the best clinical responses to thiou-

[4] There was the same ratio of iodine to protein in this gland (S. M., No. 23895) as in a large colloid goiter from an endemic goiter region which we observed some years ago. This was kindly furnished us by Dr. Frederick A. Coller of Ann Arbor. This material also did not have any physiologic activity when tested in the amount of .5 mg. of iodine.

racil were observed in the rather acute cases that had had no previous treatment with iodine. Histologically, the thyroids of those patients whose clinical and metabolic responses were prompt and complete were markedly hypertrophic and hyperplastic with practically no colloid. Patients who had received iodine previous to thiouracil treatment made much slower responses to the drug. In general the histology of the thyroid glands of patients who had made delayed responses to treatment with this agent was that of minimal to moderate hypertrophy accompanied by some degree of involution.

Since the previously iodinized patients whose thyroids, even after thiouracil treatment, show some degree of involution make a slow or delayed response to thiouracil, it appears that any previously formed hormone stored in the thyroid continues to be excreted. After most of the stored hormone has been excreted, the normal thiouracil response takes place. If this conception is correct, the action of thiouracil is not to block the excretion of thyroid hormone but rather to block its synthesis from smaller components. This theory is supported by chemical and physiological studies made on thiouracilized thyroids.

As indicated above, thyroids removed from patients with Graves' disease who had been prepared with thiouracil contained one-fourth to one-third of the iodine one would expect to find in normal human thyroids or in the glands of thyrotoxic patients treated preoperatively with iodine. Moreover, such glands possess a low order of calorigenic activity as tested on myxedematous patients.

Hertz, Roberts and Salter (9) reported that the hyperplastic thyroids of patients with Graves' disease show an increased avidity for iodine when studied by means of tracer doses of radioactive iodine. One patient to whom we gave a tracer dose of radioactive iodine, before thiouracil treatment, excreted in the urine during a five-day period only 13% of the administered dose. During a similar period of observation this patient excreted in the urine more than 100% of a tracer dose of iodine which was administered 24 hours after treatment with thiouracil was started. All but one of the patients to whom tracer doses of radioactive iodine were given, one to two days before operation, and after thiouracilization, excreted more than 55% of the labelled iodine. Similar observations have been made in rats made goitrous by thiouracil (10). Though these rats had large and hyperplastic goiters their thyroid glands were unable to collect more than an average of 10% of the tracer iodine administered. It is an interesting paradox that such hyperplastic thyroids take up less iodine than does the histologically normal thyroid.

The action of thiouracil on the thyroid gland has been compared with that of thiocyanate by observing the collection of radio active iodine by the thyroid. The thyroids of rats made goitrous by the administration of potassium thiocyanate were found to take up an average of 87% of a tracer dose of radioactive iodine. Moreover, one patient, recently reported from this clinic (4), developed a large and hyperplastic goiter while taking potassium thiocyanate as treatment for hypertension. When a tracer dose of radioactive iodine was given to this patient, 26% was excreted.

We are unable to state what the mechanism of thiocyanate goitrogenesis is. However, it would appear, from our present observations that the action of thiouracil is to block the normal iodination of protein concerned in the production of active thyroid hormone.

The goitrogenic effects of thiouracil and related drugs, described by the Mackenzies (1) and by Astwood et al (2), were not reproducible in hypophysectomized rats. Furthermore the Mackenzies observed that rats made goitrous by these agents presented changes in the pituitary glands similar to those found in the pituitaries of thyroidectomized rats. The thyroid hyperplasia, then, is probably due to some stimulation by the pituitary thyrotropic hormone.

Dempsey (11) has demonstrated by *in-vitro* techniques that thiouracil will inhibit peroxidase activity in the thyroid. He suggested that diminished peroxidase activity would interfere with the conversion of diiodotyrosine to thyroxine.

In the light of our observations on thyrotoxic patients treated with thiouracil, and on rats made goitrous by the administration of this drug, we suggest the following theory to explain the goitrogenic action of this agent.

Thiouracil produces a block of those enzyme systems of the thyroid which are necessary to the iodination of thyroid protein. This results, then, in the production of a physiologically inactive incretion. Meanwhile the stored hormone in the thyroid continues to be delivered until all of it has been utilized. After the gland has been emptied of its active thyroglobulin, the basal rate of oxygen consumption by the peripheral cells falls. Either the low metabolism *per se* or the loss of the inhibiting effect of thyroid hormone upon the pituitary results in an increased elaboration of pituitary thyroid-stimulating hormone which in turn causes thyroid hyperplasa.[5]

SUMMARY AND CONCLUSIONS

The effects of administration of thiouracil, as we have observed them in 19 patients with Graves' disease, are as follows.

1. Lowering of basal metabolic rate following a curve similar to that resulting from iodine administration.

2. Relief of symptoms similar to that resulting from iodine administration.

3. Increase of hyperplasia of the thyroid with loss of colloid and increase in vascularity. In some instances increased lymphoid hyperplasia.

4. Decreased avidity for iodine by the thyroid gland as shown by greatly impaired collection of radioactive (tracer) inorganic iodine, with increased elimination in the urine.

5. Impairment in the physiologic activity of the thyroids of persons treated with the drug as tested on patients with myxedema.

6. In persons previously treated with iodine, effects numbered 1 and 2 are delayed.

It is believed that these facts are consistent with the theory that thiouracil acts by preventing (or blocking) the utilization of iodine in the synthesis of thyroid hormone within the thyroid gland. Under the influence of thiouracil no new active thyroid hormone is produced.

Cessation of active thyroid hormone production is believed to stimulate the thyrotropic activity of the pituitary and this in turn causes further hyperplasia of the thyroid which, however, does not overcome the thiouracil block to active thyroid hormone production.

[5] For a diagrammatic exposition of this hypothesis see Rawson, Tannheimer, and Peacock (10).

REFERENCES

1. Mackenzie, C. G. and J. B. Mackenzie. Effect of sulfonamides and thioureas on the thyroid gland and basal metabolism. *Endocrinol.* 32: 185. 1943.
2. Astwood, E. B., J. Sullivan, A. Bissell and R. Tyslowitz. Action of certain sulfonamides and of thiourea upon the function of the thyroid gland of the rat. *Endocrinol.* 32: 210. 1943.
3. Astwood, E. B.: The chemical nature of compounds which inhibit the function of the thyroid gland. *J. Pharmacol. & Exper. Therap.* 78: 79. 1943.
4. Rawson, R. W., S. Hertz and J. H. Means: Thiocyanate goiter in man. *Ann. Int. Med.* 19: 829. 1943.
5. Astwood, E. B.: Treatment of hyperthyroidism with thiourea and thiouracil. *J. Am. Med. Assn.* 122: 78. 1943.
6. Williams, R. H. and G. W. Bissell: Thiouracil in the treatment of thyrotoxicosis. *N. England J. Med.* 229: 97. 1943.
7. Moore, F. D., D. N. Sweeney, Jr., O. Cope and R. W. Rawson: Value of thiouracil in preparing patients with Graves' disease for operation. *In Preparation.*
8. Means, J. H. and J. Lerman: The curves of thyroxine decay in myxedema and of iodine response in thyrotoxicosis; Their similarity and its possible significance. *Ann. Int. Med.* 12: 811. 1938.
9. Hertz, S., A. Roberts, and W. T. Salter: Radioactive iodine as an indicator in thyroid physiology. IV. The metabolism of iodine in Graves' disease. *J. Clin. Investigation* 21: 25. 1942.
10. Rawson, R. W., J. F. Tannheimer and W. C. Peacock: The uptake of radioactive iodine by the thyroids of rats made goitrous by potassium thiocyanate and by thiouracil. *Endocrinol.* In press.
11. Dempsey, E. W.: Fluorescent and histochemical reactions in the rat thyroid gland at different states of physiological activity. *Endocrinol.* 34: 27. 1944.

Report of Two Cases of Myxedema with Extreme Hypercholesteremia; One Complicated by Xanthoma Tuberosum

LEELA STEVENS CRAIG, M.D.,
H. LISSER, M.D., AND MAYO H. SOLEY, M.D.

From the Division of Medicine, University of California Medical School, San Francisco, California

A MODERATE elevation of the blood cholesterol level is an almost constant and diagnostic finding in clinical myxedema. Hurxthal and Simpson (1) concluded that the average normal fasting value for plasma cholesterol is 180 mg. per 100 cc. and that a level of 300 mg. of cholesterol per 100 cc. of blood is well above the average range. Of 404 patients with cholesterol values of 300 mg., or more who were studied over a 7-year period, the majority had a value below 500 mg. and in only 4 cases was it above 700 mg. Sixty-four per cent of those with elevated cholesterol levels were thought to be examples of thyroid deficiency. Escamilla (2) reported the case of a patient with severe myxedema who had an initial fasting level of 953 mg. per cent and a B.M.R. of 38 per cent minus. We are reporting the cases of two patients with spontaneous myxedema whose fasting blood cholesterol levels were 667 mg. per cent and 926 mg. per cent; both demonstrated the inverse ratio of cholesterolemia and basal metabolic rates, the latter being 38 and 35 per cent minus, respectively. The second patient also had xanthoma tuberosum, which, though said by numerous authors to occur in myxedema, is to our knowledge (3, 4) reported in only two such cases in the literature.

CASE REPORTS

Our presentation of 2 cases of primary adult myxedema is summarized and portrayed in the accompanying illustrations. Both patients first were studied under controlled conditions in the hospital and subsequently observed in the Medical Clinic of the University of California Medical Center.

Case I; I. R. (U 84093) is that of a 61-year-old woman whose symptoms of myxedema developed gradually over a period of 10 years, with marked aggravation for the last 5 months. As is clearly apparent from the photographs (fig. 1, 2) the appearance of the patient was strikingly altered during the first 7 weeks of treatment with thyroid substance. Her symptoms were comparably ameliorated. She lost weight and began to have more energy and endurance and a feeling of warmth. Her mucous membranes were no longer pale and swollen; her tongue became smaller and she spoke more rapidly; there was an improvement in her hearing, both subjectively and objectively. Her cardiogram, initially "atypical and abnormal," became completely normal under therapy. The hypercholesteremia of 667 mg. per cent dropped to 191 mg. per cent while the B.M.R. rose from 38 per cent minus to 4 per cent minus (table I).

TABLE I. PERTINENT LABORATORY FINDINGS IN CASE I

Date	May 1942	June 1942	July 1942
Cholesterol	**667 mg. %**	**416 mg. %**	**191 mg. %**
B. M. R.	38%−	20%−	4%−
Resting pulse	66	82	84
Blood pressure	130/85		150/90
Weight lbs.	121.1		114.2
Thyroid dosage, per day	½ grain	1 to 1½ grains	2 grains

Case II; E. A. M. (U 83084) (fig. 3, 4) is that of a 49-year-old man who came to the clinic requesting surgery for a hernia which had been present since his childhood. He had noticed a sudden onset of yellow nodules on his hands and back about 18 months before entry; later, similar lesions developed over his elbows and knees. His only other presenting complaint was fatigue, though in response to leading questions he

admitted symptoms of hypothyroidism for 2 years. He denied all symptoms of gall-bladder or liver disease and all gastro-intestinal complaints except constipation. His liver was enlarged to 6 cm. below the right costal margin.

Eighteen months before entry he had been given U.S.P. Thyroid, 4 grains (.26 gm.) daily for 3 months with relief of symptoms, including the disappearance of the xanthomatous nodules. He stated that he had been very uncomfortable even when the dose of thyroid was reduced to 1 grain (.065 gm.) daily. About 3 months after he stopped taking thyroid substance the nodules recurred (fig. 5) and continued to enlarge despite sporadic small doses of thyroid ($\frac{1}{4}$ grain) daily which he took haphazardly during the year before he first consulted us.

He had had no thyroid substance for one week prior to our initial investigation. After our diagnostic studies were completed it seemed prudent to begin treatment with unusually small doses of thyroid substance in order to avoid the reactions he claimed to have had when he took 1 or more grains daily. Accordingly, the initial dose was $\frac{1}{2}$ grain daily; this was increased gradually to $1\frac{1}{2}$ grains daily. He lost weight, was relieved of constant fatigue, gained strength, and was no longer intolerant to cold. The thickened vocal cords and the brassy voice returned to normal; macroglossia and slow speech disappeared. Bilateral nerve deafness similar to boilermakers' disease was also improved. His dyspnea after exertion was relieved completely. The liver receded to a normal size after one month. After 3 months the skin lesions were regressing. Most of the important laboratory data are charted (table II). The blood cholesterol fell from the very high level of 926 mg. per cent in April, 1942 to 196 mg. per cent in July, 1942, while the B.M.R. rose from 35 per cent minus to 8 per cent plus during this same interval. An electrocardiogram which was taken at the first visit showed abnormalities, possibly suggesting

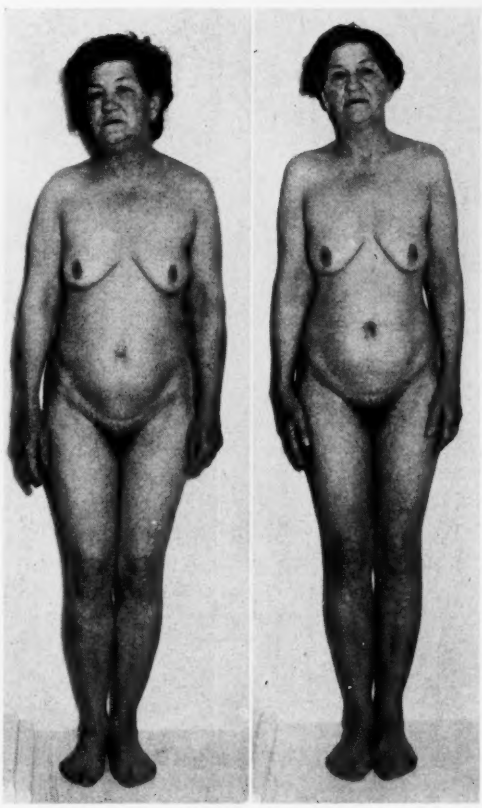


FIG. 1. Case I. Left, appearance in May, 1942 before treatment. Right, appearance in July, 1942 after 7 weeks' treatment. Note more erect posture. Pubic and axillary hair is increased.

FIG. 2. Case I. Above, appearance in May 1942. Note puffy features, dull porcine expression, coarse wrinkles, myxedematous eyelids and puffy ear lobes.

Below, appearance in July 1942, after seven weeks' treatment. Appears younger and livelier; brows are thicker and nasolabial folds deeper. The skin is finer.

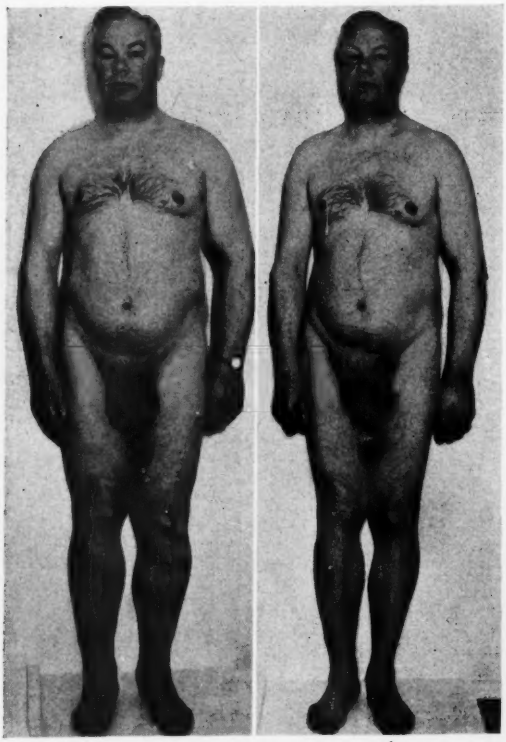


FIG. 3. Case 2. Left, appearance before treatment. Moderate generalized hypothyroid obesity, fatigue posture, edema of lower legs.

Right, after 8 months' treatment with thyroid, 1 to 2 grains daily. Improved posture, more hair on legs, no edema.

coronary disease; after one month of treatment the cardiogram was reported as "more nearly normal." The Rose Bengal studies of liver function, made prior to instituting thyroid therapy, showed evidence of liver damage; the tests became normal after adequate thyroid therapy.

Rose Bengal Retained

	Before treatment	*After 1 year*	*Normal range*
8 min.	74% retained	57% retained	55% retained
16 min.	56% retained	34% retained	35% retained

TABLE II. PERTINENT LABORATORY FINDINGS IN CASE II

Date	Apr. 1942	July 1942	Jan. 1943
Cholesterol	**926 mg. % serum creamy**	**196 mg. %**	**340 mg. %**
B. M. R.	35%−	8%+	15%−
Resting pulse	70	80	62
Blood pressure	136/76	94/60	90/60
Weight lbs.	235.4	211.2	210
Thyroid dosage, per day	1 to 2 grains	1½ grains	2 grains

DISCUSSION

These two cases of clinical myxedema had unusually high levels of plasma cholesterol concomitant with lowered basal metabolic rates. In both cases the symptoms of myxedema disappeared after treatment with thyroid substance and the plasma cholesterol fell to normally accepted levels. There was a reciprocal change between the fall in plasma chloesterol level and the elevation of the basal metabolic rate. This seems conclusive evidence that the remarkably high initial cholesterol levels were associated with the myxedema. Indeed, Hurxthal and Simpson (1) claim that "if a blood cholesterol value cannot be lowered by at least

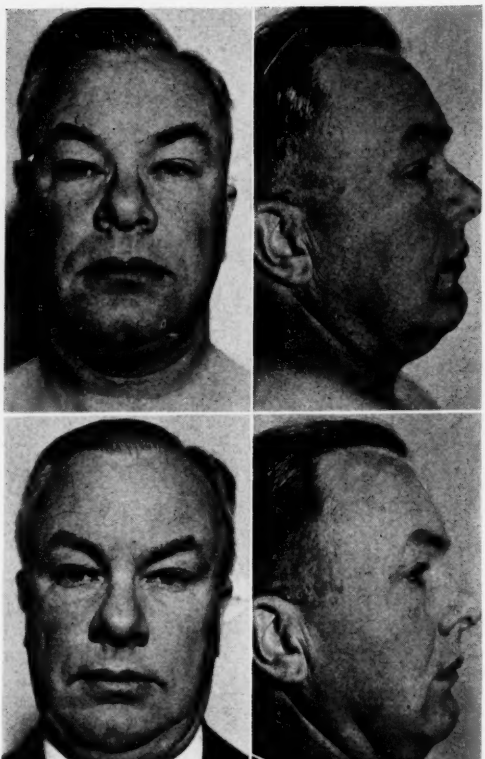


FIG. 4. Case 2. Above, appearance in April 1942. Note myxedematous skin, puffiness of all features, narrow eye slits and pressure lines from glasses.

Below, after treatment. Skin smoother, thinner, firmer; lips thinner. Note widened palpebral apertures, alert expression and change in shape of nose.

40% of the original value on this dose (2 grains U.S.P. thyroid), the probability of its elevation being due to thyroid deficiency is considerably lessened." The skin lesions of xanthoma tuberosum which were a complication of Case II, regressed more slowly than the manifestations of myxedema.

Hypercholesteremia is found frequently in numerous conditions other than myxedema. These include arteriosclerosis and many of the xanthomatoses. There are at least three prevalent theories to explain the hypercholesteremia of myxedema. Lowered cholesterol excretion may cause increased retention and higher plasma levels if it does not keep pace with the endogenous and exogenous supplies of cholesterol, as suggested by Thannhauser (7, 8). Some disturbance of the enzyme system of lipid metabolism may result in over-production or under-utilization or both (9). Blood-cholesterol levels may change as cholesterol is shifted from plasma to tissues, a reflection of the rate at which fatty acids are being transported for oxidation and storage (10). The observations in our cases might be explained by any or all three of these theories.

It is significant that Case II represents a secondary xanthomatosis, namely, xanthoma tuberosum, a benign symptomatic, nodular-eruptive form of xanthomatosis, probably due to hyperlipemia. Though it was not possible to make complete lipid studies, the milky appearance of the serum disappeared with the reduction of the hypercholesteremia. As is usual in cases of xanthoma tuberosum, the non-tender, yellowish nodules occurred predominantly on the extensor surfaces, both superficially and along the tendon sheaths and on the palms of the hands. Their regression was definitely correlated with control of the myxedema symptoms by treatment with thyroid substance alone. Until there is a better understanding of the metabolism of lipids, various definitions and interpretations will exist. Most authorities agree that xanthoma tuberosum is a secondary disorder of the skin; they believe that the skin lesions usually disappear as the basic disturbance and the associated hyperlipemia are corrected. Montgomery (whose discussion contains a good bibliography) noted the frequent association of xanthoma tuberosum with severe cardiovascular or hepatic disease. The results of thyroid therapy in the second case reported by us suggest what appears to be a significant correlation of improvement in all of the following factors—the clinical aspects of myxedema, the extreme hypercholesteremia and the laboratory and physiologic evidence of disease of the liver.

A patient in whom the basal metabolic rate and liver function tests were normal was reported by McGavick and Shepardson (12) as having "Idiopathic xanthoma disseminatum with hypercholesteremia." In this patient the

FIG. 5. Case 2. Left, shows firm, discrete, non-tender, yellow xanthematous nodules. Right, after treatment.

effect of thyroid medication was inconclusive in its effect on the hypercholesteremia and the xanthomatous lesions. In the case of xanthoma tuberosum and myxedema reported by Sweitzer and Winer (4), the administration of thyroid substance produced no improvement in the skin lesions during a few months' period, despite a return to normal of both cholesterol and basal metabolic levels. The case reported by Christie, Lyall and Anderson (3) showed similar metabolic response, but the skin lesions were much improved after six months; their patient had reported symptoms of gall-bladder disease for twenty years, but had had manifestations of myxedema and xanthoma tuberosum for only one year; however, no symptoms of gall-bladder disease occurred while under thyroid therapy.

SUMMARY

Two cases of myxedema with hypercholesteremia are considered worthy of record because of three noteworthy features.

1. The plasma cholesterol levels were unusually high.

2. The inverse ratio of the blood serum cholesterol and the basal metabolic rate in myxedema received confirmation.

3. Additional data on the functional pathology of xanthoma tuberosum were obtained.

REFERENCES

1. HURXTHAL, L. M., AND H. N. SIMPSON: Blood in myxedema—hypercholesteremia. *J. Clin. Endocrinol.* 1: 450. 1941.
2. ESCAMILLA, R.: Carotinemia in myxedema. *J. Clin. Endocrinol.* 2: 33. 1942.
3. CHRISTIE, J. F., A. LYALL AND T. E. ANDERSON: Case of xanthoma multiplex, associated with hypothyroidism. *Brit. J. Dermatol.* 42: 429. 1930.
4. SWEITZER, S. E. AND L. H. WINER: Xanthoma tuberosum and myxedema; report of a case. *Arch. Dermat. & Syph.* 42: 419. 1940.
5. BLOOR, W. R.: The determination of small amounts of lipid in blood plasma. *J. Biol. Chem.* 77: 53. 1928.
6. GREENE, A. M.: Iodine and cholesterol metabolism in patients with primary myxedema. A clinical and experimental study with a report of results and treatment. *Arch. Int. Med.* 67: 114. 1941.
7. THANNHAUSER, S. J.: Lipidoses: Diseases of the cellular lipid metabolism. London, 1940. Oxford University press.
8. THANNHAUSER, S. J.: Cholesterol metabolism and the different groups of xanthomatous diseases. *Proc. California Acad. Med.* 6: 97. (1937–1938).
9. SPERRY, W. M.: The biochemistry of the lipoidoses. *J. Mt. Sinai Hosp.* 9: 799. 1942.
10. FLEISHMAN, W. AND H. B. SHUMACKER, JR.: The relationship between serum cholesterol and total body cholesterol in experimental hyper- and hypothyroidism. *Bull. Johns Hopkins Hosp.* 71: 178. 1942.
11. MONTGOMERY, H.: Cutaneous manifestations of diseases of lipid metabolism. *M. Clin. North America* 24: 1249. 1940.
12. MCGAVICK, T. H. AND H. C. SHEPARDSON: Xanthoma accompanied by hypercholesteremia, occurring in an otherwise normal individual, and in an individual with acromegaly and diabetes. *Ann. Int. Med.* 7: 582. 1933.

Effect of Estrogenic Hormone on Hyperthyroidism

AARON A. FARBMAN, M.D.

From the Department of Surgery, North End Clinic, Detroit, Michigan

THAT a relationship exists between the ovary and the thyroid has long been recognized. At the onset of puberty, during pregnancy and lactation and at the menopause the thyroid often increases in size. In hyperthyroidism, irregular menstruation, menorrhagia and particularly amenorrhea are frequently observed. These menstrual disturbances, particularly menorrhagia, also occur in hypothyroidism. These disorders appear to be due to the non-specific or perhaps the specific action of the thyroid hormone on gonadal cells. Uotila (1) found that thyroxin produces atrophy of the seminal vesicles of the rat, probably by depressing the output of gonadotropic hormones of the anterior lobe of the pituitary. On the other hand Howell, Drips and Fisher (2) have observed excessive amounts of gonadotropic principles in the urine of both hyperthyroid and hypothyroid subjects. In any event there is considerable evidence that the gonads are affected by the thyroid. That conversely, the thyroid is affected by the gonads has recently attracted considerable interest and is the basis for this clinical study.[1]

The results and interpretation of experimental data, clinical observations and investigations on this subject are for the most part contradictory and uncertain. Rogers (3) reported cases of Basedow's disease occurring unexpectedly after castration. Lederer (4) described a case in a female 36 years old who had a subtotal thyroidectomy for exophthalmic goiter followed later by castration with subsequent return of thyrotoxicosis. Case 8 below has a similar history. On the other hand Spence (5) points out that sexual infantilism occurs in cretinism and that impotence, sterility and atrophy of the genitalia are seen in myxedema. These conditions are corrected by administration of thyroid. To complicate the picture, sterility and sexual atrophy also occur in toxic goiter (6). The effect of castration on thyroid activity has been variously reported. Anderson and Kennedy (7) reviewed the published papers on this subject up to 1933 and contributed well controlled experiments of their own on rabbits, guinea pigs and rats. They were in agreement with most of the published work in that atrophy of the thyroid occurred after gonadectomy; in their own work this occurred eight weeks after the operation. Histologically the thyroid follicles were smaller than those of the controls, contained denser colloid and were surrounded by low or flat epithelium. Yet Loeser (8) repeatedly found hyperplasia of the thyroid in guinea pigs after removing their ovaries.

The effect of estrogenic hormone on thyroid activity in animals has also been studied, again with varying results. Laqueur, Hart and de Jongh (9) found that the injection of estrogenic hormone increased the basal metabolism of normal or ovariectomized rats from 15 to 20% in two or three days. Tagliaferro (10) found, however, that estrin administered for 5 to 10 days produced hyperactivity of the thyroid, but when it was continued for 20 days or more, the opposite effect was produced. Sherwood, Savage and Hall (11) in 1933, Sherwood and Bowers in 1936 (12) and Sherwood (13) in

[1] The author wishes to thank Drs. Paul Starr, T. C. Sherwood and J. H. Means for their helpful comments after previewing this study.

1940 made extensive experimental studies on the effects of amniotin, theelin and later stilbesterol on the basal metabolism of experimental hyperthyroid rats and rabbits. They found that 10–800 Rat Units of amniotin lowered the metabolic rates of rabbits 37% when these animals were fed with thyroid and lowered the rates of rats 42% below normal in oöphorectomized animals and 20% below normal in intact animals. They also found that the basal metabolism of experimental hyperthyroid animals when treated with estrogenic hormone returned to normal in half the time taken by the untreated ones. Zain (14, 15), Gessler (16, 17) and Laprida (18) also decreased experimental hyperthyroidism with injections of estrogenic hormone and Kunde, D'Amour and Carlson (19) found the metabolism of normal adult dogs to be slightly lowered by continuous administration of estrin with production of estrus. Aron and Benoit (20) found that large doses of estrin would prevent the hyperthyroidism that was otherwise produced by pituitary thyrotropic hormone. Spence (5) and later Elmer, Giedosz and Scheps (21) made similar observations.

Interesting observations have also been made clinically. Hitchcock and Wardwell (22) studied a group of normal women in whom the basal metabolic rate was determined frequently throughout the menstrual cycle. The metabolic rate was lower during menstruation and midway between periods but higher premenstrually. Most investigators have reported a definite rise in blood and urinary estrins around the time of ovulation and a slight fall just before the onset of bleeding (25). This would indicate that in the normal individual thyroid activity is somewhat increased when blood and urinary estrin is low, and vice-versa.

Jonas and Markalous (23) studied the 24-hour urine excretion of estrogenic substance and made tests in castrate mice. They found a lower excretion of estrin in thyrotoxicosis but not in proportion to the metabolic rate or to the disturbance in menstrual cycles. In two cases studied after remission there was increase in estrin excretion.

Reports on the effect of estrogenic hormone in human thyrotoxicosis are very scanty. The number of cases are few; dosages and duration of treatment different, with consequent variation in results. Marine (24) and Tagliaferro (10) both point out that the variation in the periods of estrin administration may be a factor in producing different effects. Starr and Patton (26, 27) in 1934 and 1935 obtained lasting remission in 7 of 13 cases of hyperthyroidism treated with pregnancy-urine extract (Antuitrin S, 100 R.U. and Theelin, 50 R.U.) daily or three times a week before or after the menses for four or five months. The patients who responded had normal ovaries. Five of the failures occurred in either post-menopausal women or women with diseased ovaries. The sixth was a male. These authors believe, therefore, that the pregnancy urine extract stimulated the production of estrin in the ovary and that this in turn inhibited the thyroid. In 1936 Spence (5) treated six severely toxic cases with estrogenic hormone. They were given bed rest for 14 to 32 days before treatment was started. Two received 50,000 International Units of dimenformon daily for 12 days and two others for 21 days. The fifth and sixth cases received by mouth 250,000 International Units of menformon in divided doses for 21 days. There was very little if any inhibition produced on the toxic thyroid as indicated by frequent basal metabolic rates. Lederer (4) in 1939, in addition to an excellent review of the literature, reported one case treated with large doses of folliculin for 18 weeks with complete and lasting remission. This patient, a woman 36 years old, had a subtotal thyroidectomy for exophthalmic goiter. Her menses had always been regular until thyrotoxic symptoms appeared, when they became scanty. Several years after operation she developed a chronic pelvic infection which was treated by total hysterectomy and bilateral oöphorectomy. Six months later, thyrotoxicosis returned. Radiotherapy, iodine, diiodotyrosine, sedatives and small doses of folliculin failed. She was then treated with large doses of folliculin: 250,000 International Units in five divided doses the first week; 200,000 the second and third week; 150,000 the fourth week; 100,000 the fifth week; and 50,000 per week from the sixth to the eighteenth week—a total of 1,300,000 International Units. A basal metabolic rate of

plus thirty returned to normal, the patient gained weight and became symptom-free. Goldman, Goldman and Kurzrok (25) studied a series of eight cases of hyperthyroidism. Five of these were assumed to be cases arising with the climacteric. Total doses ranging from 500,000 to 750,000 International Units of Progynon B were given over a short period of time. These patients were all hospitalized. Lasting remission occurred in three of the five menopausal cases. The others were not benefited by this treatment although some inhibition was observed. Storck and Sabatier (28) and Storck and Holcombe (29) have recently observed beneficial results with estrogenic substance in the pre-operative and post-operative treatment of 11 cases of hyperthyroidism.

A STUDY OF NINE CASES

Nine cases of thyrotoxicosis in the female were treated with large doses of estrone.[2] Total dosage ranged from 210,000 to 3,410,000 International Units given over a period of 6 weeks to 16 months. Subsequent observations were made over a period of 17 to 26 months. All cases were ambulatory except Case 9, one of thyroid crisis treated in the Hospital. Sedatives and iodine were not given.

Table I shows the age, diagnosis, relative severity, total dosage, duration of treatment, subsequent observations and end results. The effect of treatment on the basal metabolic rate and blood cholesterol is shown in charts 1 to 9.

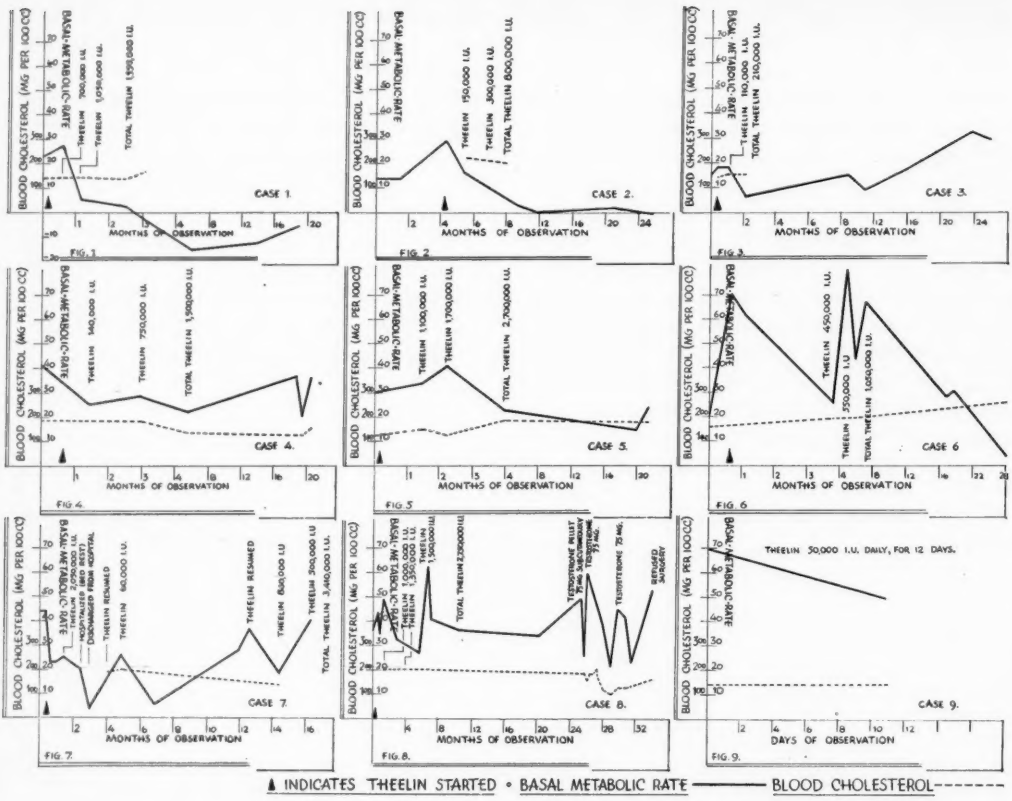
RESULTS

Of the nine cases studied, two (Cases 1 and 2) showed a complete remission without re-

[2] The estrone used in this study was theelin which was generously supplied by Parke, Davis and Co., Detroit, Michigan.

TABLE I

Case	Age	Diagnosis	Duration of Toxic Symptoms	Total Dosage of Theelin in International Units	Duration of Treatment	Duration of Observations After Treatment	Results
1	17	Exophthalmic goiter (mild)	2 yrs.	1,550,000	2⅓ mos.	17 mos.	Complete remission without relapse
2	45	Post-operative exophthalmic goiter (mild residual hyperthyroidism)	6 mos.	800,000	3 mos.	25 mos.	Complete remission without relapse
3	28	Toxic adenoma (mild)	5 mos.	210,000	1½ mos.	26 mos.	Complete remission with relapse after 16 mos.
4	19	Exophthalmic goiter (moderately severe)	2¼ yrs.	1,500,000	4 mos.	20 mos.	Slight response during treatment with relapse 6 mos. after treatment
5	38	Toxic adenoma (moderately severe)	Several mos.	2,700,000	3½ mos.	17 mos.	No response during treatment. Slight improvement after treatment
6	49	1. Toxic adenoma (moderately severe) 2. Syphilis	7 mos.	1,050,000	5½ mos.	23 mos.	No response during treatment. Spontaneous remission 23 mos. after treatment
7	20	1. Toxic adenoma (moderately severe) 2. Polyglandular disturbance	10 mos.	3,410,000	16 mos.	0	Slight response with relapse soon after each course. No response after last course. Subtotal thyroidectomy with uneventful recovery
8	44	Recurrent toxic adenoma (severe) Subtotal thyroidectomy 12 years previously	18 mos.	2,750,000	10 mos.	24 mos.	No result Refused surgery
9	27	Thyroid crisis in hospital	17 mos.	600,000	12 days	0	No result. Lugolized. Subtotal thyroidectomy. Uneventful recovery.



Case 1: Mild thyrotoxicosis with diffuse enlargement of the thyroid in a girl 17 years old. Total dosage 1,550,000 International Units Theelin given in two-and-a-third months. Complete remission without relapse for 17 months after treatment.

Case 2: Mild residual hyperthyroidism at the menopause persisting for six months after subtotal thyroidectomy for exophthalmic goitre. Total dosage 800,000 International Units Theelin given in three months. Complete remission without relapse for 25 months after treatment.

Case 3: Mild toxic adenoma in a female 28 years old. Total dosage 210,000 International Units Theelin given in one-and-a-half months. Complete remission with relapse 16 months after treatment.

Case 4: Moderately severe exophthalmic goitre in a girl 19 years old. Total dosage 1,500,000 International Units Theelin given in four months. Slight reduction of basal metabolic rate during treatment with relapse soon after treatment.

Case 5: Moderately severe toxic adenoma in a woman 38 years old. Total dosage 2,700,000 International Units Theelin given in three-and-a-half months. Slight reduction in basal metabolic rate during treatment and for 17 months after treatment.

Case 6: Moderately toxic adenoma at the menopause associated with syphilis. Total dosage 1,050,000 International Units Theelin given in five-and-a-half months. No response during treatment. Basal metabolism dropped to normal spontaneously 23 months after treatment.

Case 7: Moderately severe toxic adenoma in a young obese woman 20 years old with evidence of profound polyglandular disturbance. Total dosage 3,410,000 International Units Theelin given in 16 months. Some reduction of basal metabolism during treatment with relapse soon after each course. No response during last course. Subtotal thyroidectomy with uneventful recovery.

Case 8: Severe recurrent toxic adenoma at the menopause 12 years after thyroidectomy and 18 months after hysterectomy and bilateral salpingectomy. Total dosage 2,750,000 International Units Theelin given in ten months. No response After 25 months of observation three 75 mg. Testosterone pellets were implanted subcutaneously during the following four months. No response. Refused surgery.

Case 9: Thyroid crises in a female 27 years old. Total dosage 600,000 International Units Theelin given in twelve days. Slight reduction of basal metabolism. Subsequent lugolization and subtotal thyroidectomy with uneventful recovery.

lapse 17 and 25 months after treatment. Case 1 was of mild exophthalmic goiter in a young girl of 17, and Case 2 was of postoperative exophthalmic goiter with mild residual symptoms persisting for six months before therapy was started.

The effect on the basal metabolic rate is discussed below. Blood-cholesterol changes (charts 1 to 9) were inconsistent and insignificant. There was relatively no change in three cases, slight increase in three and slight decrease in three. There was no change in size in the nodular goiters and perhaps only slight diminution in size in the diffuse hyperplastic variety. Exophthalmos was unchanged in Case 2, slightly decreased in Case 4. Three cases of oligomenorrhea (1, 4 and 5) and one case of amenorrhea (Case 3) became normal after treatment. Two cases (7 and 8) remained unchanged. In two cases (2 and 6) the subjects were in the menopause and Case 9 was one of thyroid crisis studied for only 12 days. All the patients inproved subjectively during treatment except Case 9. There were no harmful effects from this form of therapy.

DISCUSSION

It can readily be seen that massive doses of estrone do not directly lower the basal metabolism nor change the disease in severe thyrotoxicosis (Cases 8 and 9). This is also true with the moderately severe cases (Cases 4, 5, 6 and 7) except that a slight, transient decrease in the basal metabolic rate was observed in Cases 4 and 7 during treatment. There was no response in Case 6 during treatment, but a spontaneous remission occured 23 months after therapy. It is difficult to believe that the estrone was responsible for this effect. There was a rapid and lasting response in the mild hyperthyroids (Cases 1, 2 and 3) and particularly in Cases 1 and 2. These cases might have improved spontaneously without any therapy. Yet the rapid improvement of toxic signs and symptoms lasting 24, 6 and 5 months respectively did not appear to be coincidental.

As to the mechanism involved in this relationship one can only speculate. It is difficult to suppose that inhibition is produced by suppressing the thyreotropic pituitary hormone, for it has been shown that thyreotropic-hormone production is already reduced in hyperthyroidism (20). Sherwood (30) has recently produced a lowering of the basal metabolism in thyroidectomized male rats, fed with desiccated thyroid, by administration of estrogenic substance. He believes that the results indicate a direct hormone antagonism in the tissues and that it is not due to an estrogenic action upon the thyroid. This suggests its further consideration in the treatment of postoperative residual symptoms.

SUMMARY

Results of animal experimentation and clinical observation on the effect of estrogenic hormone on hyperthyroidism reported in the recent literature have been, for the most part, contradictory and confusing. The purpose of the present study was to observe what effect, if any, large doses of estrogenic hormone had on thyrotoxicosis during and after treatment.

Nine cases in various degrees of thyrotoxicosis in females were treated with large doses of theelin. Total dosage ranged from 210,000 to 3,410,000 International Units given over a period of six weeks to 16 months. Subsequent observations extended over a period of 17 to 26 months. Eight cases were ambulatory. The ninth was a case of thyroid crisis observed in the hospital for 12 days.

Except for a slight transient decrease in the basal metabolic rate in two of the moderately severe cases, the treatment did not directly lower the basal metabolism nor change the disease.

There was, however, a rapid and lasting response in two mild hyperthyroids. One was a girl of 17 with a small exophthalmic goiter and mild toxic symptoms. The other was a postoperative exophthalmic goiter in a woman of 45 who had persistent residual symptoms for six months after operation. Both had a prompt and complete remission during treatment with no relapse during 17 and 25 months respectively of subsequent observation.

Large doses of estrogenic hormone seem to have some inhibitory effect on the thyroid but not enough to be apparent in cases of severe and moderately severe toxicity. It is therefore suggested that this effect be more extensively studied in the mild forms of hyperthyroidism: (1) postoperative residual hyperthyroidism, (2) borderline or mild thyrotoxicosis with little or no enlargement of the thyroid gland, (3) hyperthyroidism arising during the menopause, and (4) in the preoperative and postoperative treatment of surgical cases.

REFERENCES

1. UOTILA, U. U.: The regulation of thyrotropic function by thyroxin after pituitary stalk section. *Endocrinol.* 26: 129. 1940.
2. HOWELL, L. P., D. G. DRIPS AND H. C. FISHER: The presence of excessive amounts of gonadotropic principle in the urine of patients with thyroid disease. *Am. J. Obs. & Gynec.* 41: 868. 1941.
3. ROGERS, C. C.: Symptoms and treatment of exophthalmic goitre. *J. Am. Med. Assn.* 54: 1893. 1910.
4. LEDERER, J.: Anti-thyroid action of estrogen clinically. *Rev. Belge Sc. Med.* 11: 326. 1939.
5. SPENCE, A. W.: Oestrin in toxic goitre. *Lancet* 2: 970. 1936.
6. HOSKINS, R. G.: The interrelation of the organs of internal secretion. *Am. J. Med. Sc.* 141: 374. 1911.
7. ANDERSON, D. H. AND H. S. KENNEDY: Effect of gonadectomy on adrenal, thyroid, and pituitary glands. *J. Physiol.* 79: 1. 1933.
8. LOESER, A.: Der Einfluss des Ovariums auf die Sekretion des thyreotropen Hormone der Hypophyse. *Klin. Wchnschr.* 13: 766. 1934.
9. LAQUEUR, V. E., P. C. HART AND S. W. DE JONGH: Ueber das weibliche sexual Hormon, das Hormon des oestrichen Syklus (Menformon). *Deutsche Med. Wchnschr.* 52: 1331. 1926.
10. TAGLIAFERRO, P.: Role of estrin in production of functional and structural changes in thyroid. *Folia Gynaec.* 30: 597. 1933.
11. SHERWOOD, T. C., M. SAVAGE AND J. F. HALL: The effect of amniotin on the basal metabolism of rats and rabbits. *Am. J. Physiol.* 105: 241. 1933.
12. SHERWOOD, T. C. AND L. M. BOWERS: Effect of ovarian hormone on basal metabolism of experimental hyperthyroid rats. *Am. J. Physiol.*, 115: 645. 1936.
13. SHERWOOD, T. C.: Effect of stilbesterol on basal metabolism of experimental hyperthyroid rats. *Endocrinol.* 26: 693. 1940.
14. ZAIN, H.: Thyroid and sex hormones; antithyroidal action of large quantities of estradiol benzoate. *Klin. Wchnschr.* 16: 1351. 1937.
15. ZAIN, H.: Die Beinflussung der Hyperthyreose männlicher und weiblicher Ratten durch Kastration und grosse Follekelhormonmengen. *Arch. f. exper. Path. u. Pharmakol.* 192: 486. 1939.
16. GESSLER, C.: Influence of folliculin on basal metabolic rate. *Arch. internat. de pharmacodyn. et de thérap.* 54: 263. 1936.
17. GESSLER, C.: Active antithyroidienne de la folliculine; role de l'hypophyse. *Arch. internat. de pharmacodyn. et de therap.* 55: 261. 1937.
18. LAPRIDA, Z. B.: Thesis 4705, Universidad Nacional de Buenos Aires. 1933. P. 91.
19. KUNDE, M. M., F. E. D'AMOUR, A. J. CARLSON AND R. G. GUSTAVSON: Studies on metabolism VIII. Effect of estrin injections on the basal metabolism, uterine endometrium, lactation, mating and maternal instincts in the adult dog. *Am. J. Physiol.* 95: 630. 1930.
20. ARON, M. AND J. BENOIT: Action antagoniste de la thyreostimuline prehypophysaire et de la folliculine ovarienne sur le fonctionnement thyroiden. *Compt. Rend. Soc. de Biol.* 109: 923. 1932.
21. ELMER, A. W., B. GIEDOSZ AND M. SCHEPS: L'action du testostérone et de l'œstrone dans. l'hyperthyréose expérimentale. *Compt. Rend. Soc. de Biol.* 129: 1224. 1938.
22. HITCHCOCK, F. A. AND F. R. WARDWELL: Cyclic variations in the basal metabolic rate of women. *J. Nutrition* 2: 203. 1929.
23. JONAS, V. AND E. MARKALOUS: Studium des Follikilhormons bei Hyperthyreose. *Zentralbl. f. Gynäk* 60: 2614. 1936. Abst., *Endocrinol.* 21: 309. 1937.
24. MARINE, D.: Glandular physiology and therapy. *Am. Med. Assn. Chicago*, 1935, p. 326. (Quoted by Spence (5).)
25. GOLDMAN, S. F., A. GOLDMAN AND R. KURZROK: Treatment of menopausal hyperthyroidism with estrogenic substance. N. Y. State J. Med. 40: 1178. 1940.
26. STARR, P. AND H. PATTON: Effect of pregnancy urine extract and ovarian follicular hormone on hyperthyroidism. *Endocrinol.* 18: 113. 1934.
27. STARR, P. AND H. PATTON: Observations of remissions in hyperthyroidism induced by pregnancy urine extract. *Ann. Int. Med.* 8: 825. 1935. Abst., *J. Am. Med. Assn.* 104: 1035. 1935.
28. STORCK, A. H. AND J. SABATIER: The use of estrogenic substance in the pre- and post-operative treatment of hyperthyroidism. *Ann. Surg.* 115: 825. 1942.
29. STORCK, A. H. AND R. C. HOLCOMBE, JR.: The use of estrogenic substances in the preoperative and postoperative treatment of hyperthyroidism. *Surgery* 11: 703. 1942.
30. SHERWOOD, T. C.: Effect of estrogenic substance on experimentally hyperthyroid male rats. *Endocrinol.* 29: 215. 1941.

Effect of Testosterone Propionate in a Patient with Diabetes Mellitus and Addison's Disease

CHARLES D. ARMSTRONG, M. D.

From the Department of Medicine, Stanford University School of Medicine, San Francisco, California

THE effects of the synthetic product testosterone on electrolytes and metabolism have been carefully studied (1, 2, 3) and compared with those of other steroids, the hormones arising in the gonads and adrenals (4, 5, 6). In general, it has been found that the administration of testosterone promptly depresses the urinary output of nitrogen, inorganic phosphorus, sulphates, sodium, potassium, calcium, chlorides and creatine (7, 8, 9). A fall in serum potassium and blood urea has been noted (6, 7), suggesting deposition of tissue protein (15). Longer periods of administration may raise the basal metabolic rate and cause a gain in body weight as fluid is retained (10, 11, 12), as well as an increase in the red blood cell count (13, 14, 16), a hastening of epiphyseal closure and a decrease in sperm count (8). Testosterone probably decreases protein catabolism (13), increases fat oxidation (12) and may or may not inhibit gluconeogenesis (23). A transient and unexplained lowering of glucose tolerance and decrease in liver glycogen may follow prolonged administration of methyl testosterone (16, 17, 18)—an effect not obtained with testosterone propionate, or in hypophysectomized or thyroidectomized animals.

The action of testosterone resembles that of the adrenal cortical hormone except that testosterone causes potassium retention while cortical hormone encourages its excretion and the sex hormones in general fail to replace cortical hormone in protecting adrenalectomized rats against "water intoxication" (19, 20). It is quite probable that this similarity in action arises from the similar chemical structure of the two hormones rather than from a mediation of testosterone action through the adrenal. The truth of this statement was first indicated by Thorn (5, 6) who found an inimpaired testosterone effect in adrenalectomized dogs and a 72-hour retention of sodium, chloride and water in a woman with Addison's disease after a single injection of estradiol (4). It has since been demonstrated that testosterone may also act in the presence of Simmonds' disease (21) or of a craniopharyngioma destroying all but a shred of the pituitary (3).

The present study was undertaken to elucidate the action of testosterone[1] on a patient with a pluriglandular disturbance including Addison's disease and diabetes mellitus. Two other reports along essentially similar lines (22, 23) have appeared during its preparation. Kenyon et al. (22) gave five daily doses of testosterone propionate in oil to a man and to a woman with Addison's disease, maintained on salt and desoxycorticosterone acetate. They observed a characteristic depression of urinary electrolytes and a gain in body weight; the basal metabolic rate, the fasting respiratory quotient and the concentration of serum electrolytes were unchanged in the time period studied. Talbot and co-workers (23) found testosterone propionate but not methyl testosterone an effective substitute for desoxycorti-

[1] The testosterone propionate used in these experiments was furnished by Ciba Pharmaceutical Products Inc., Summit, N. J.

costerone acetate in an eight-year-old girl with Addison's disease, moniliasis and idiopathic hypoparathyroidism. In this case there was the 11 such cases, including this one, reported by Bloomfield in 1939 (26); also two cases in which the Addison's disease preceded the diabetes.

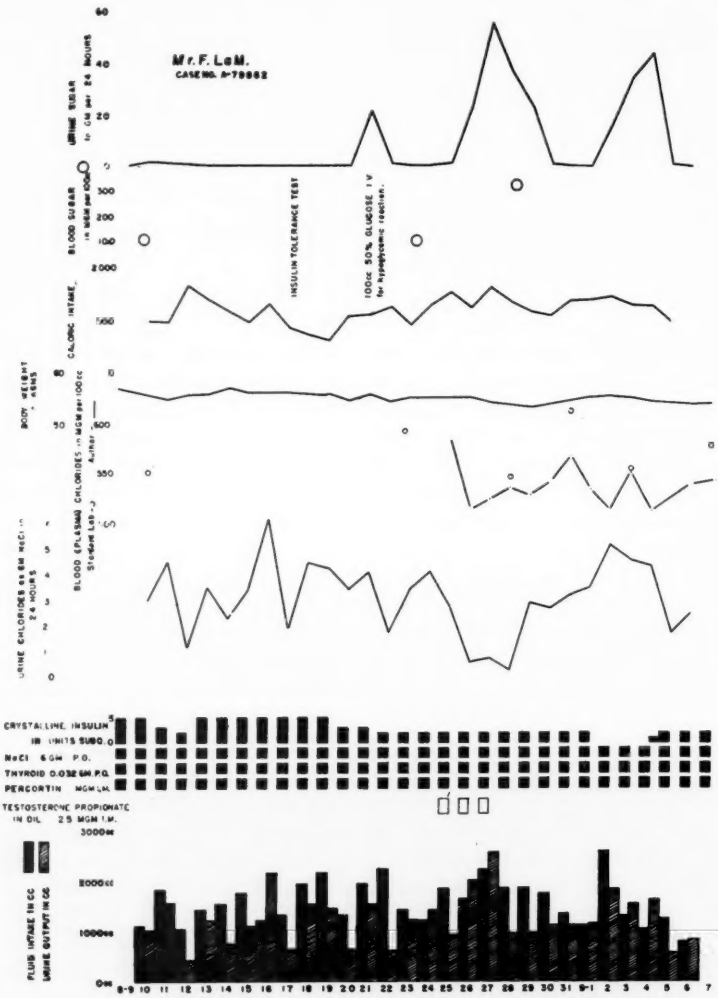


CHART 1. Mr. F. LaM. Graph showing laboratory data before, during and after testosterone administration (Table 1).

expected retention of electrolytes and a sharp fall in serum potassium but the blood sugar failed to fall as might occur with an inhibition of gluconeogenesis.

The subject of the present experiment is a pedigreed case of Addison's disease which developed under observation in a patient with diabetes mellitus. Thorn and Clinton (24) cite Nix (25) has recently reported another case of the first type.

The experimental administration of testosterone was carried out during our patient's ninth hospital admission while he was being maintained on a constant-dose schedule of insulin, percortin, salt and thyroid adjusted to his needs during the preceding five years. The

daily caloric and fluid intake was noted and the urine output was measured. The 24-hour output of sugar was determined by the Sheftel kit and the urine chloride output was found by modification of the method of Volhard. The blood chlorides were estimated daily by the method of Schales and Schales (27) and the entire study was controlled by parallel observations on another patient, a woman with myxedema, showing a typical chloride retention response (chart 2).

CASE REPORT

Mr. F. LaM., a 35-year-old electrician, first entered the hospital on April 18, 1938, because of polyuria, polydipsia and weight loss of one month's duration. His blood sugar was 560 mg. per 100 cc., his blood pressure 120/75 and he was discharged from the hospital with his diabetes controlled by a diet and 56 units of insulin a day. During the next year he felt well and gradually reduced his insulin until glycosuria was controlled by 4 units of regular insulin once or twice a day. In March, 1939, he was beset by severe weakness, dyspnea, a craving for salt and a yellow-brown discoloration of the skin and had several hypoglycemic reactions. He re-entered the hospital May 11, 1939, presenting a typical picture of Addison's disease. His blood pressure had fallen to 85/60, his blood sugar to 105 mg. per 100 cc., and his blood chlorides (as NaCl in whole blood) to 385 mg. per 100 cc. The blood urea was 57 mg. per 100 cc.; the BMR,—15 per cent. X-ray findings of the abdomen, chest and sella turcica were not remarkable. A skin biopsy at this time as well as a subsequent biopsy revealed no evidence of hemochromatosis. Eschatin, salt and later desoxycorticosterone acetate brought about a marked clinical improvement, the Eschatin alone producing a glycosuria and glycemia (26).

In July, 1940 the patient was taking 0.3 cc. (1.5 mg.) of percortin, 3 gm. of salt, and 4 units of crystallin insulin with a free diet. He felt well and was able to work; his blood pressure was 82/50; blood urea, 34 mg. per 100 cc.; blood sugar, 54 mg. per 100 c.c; whole blood chlorides, 574 mg. per 100 cc.; and BMR, −26 per cent. By January, 1942 the patient's blood pressure was 110/88; blood urea, 36 mg. per 100 cc.; plasma chlorides, 510 mg. per 100 cc.; and BMR,−42 per cent.

In July, 1942 he entered the hospital in almost moribund condition after a period characterized by hypoglycemic reactions and increasing lethargy. The blood pressure was 110/80; blood urea, 21 mg. per 100 cc.; blood sugar ranged from 114 to 35 mg. per 100 cc.; plasma chlorides, 528 mg. per 100 cc.; and the BMR was −51 per cent. Ten cc. of Eschatin resulted in an increase in appetite and activity; the blood sugar rose to 444 mg. per 100 cc. The chest and skull as disclosed by x-rays remained normal. The patient was discharged on a daily ration of 0.8 cc. of percortin, 0.032 gm. of thyroid, 8–10 gm. of NaCl, and 2–4 units of crystalline insulin by test. In September, 1942 he was taking percortin 0.4 cc., NaCl 6 gm., thyroid 0.032 gm., and 3–4 units crystalline insulin; his blood pressure was 136/90. Urine chloride values ranged from 2 to 15 gm. NaCl per 24 hours.

On August 9, 1943, the patient re-entered the hospital for investigation of a weight loss of 22 lb. He

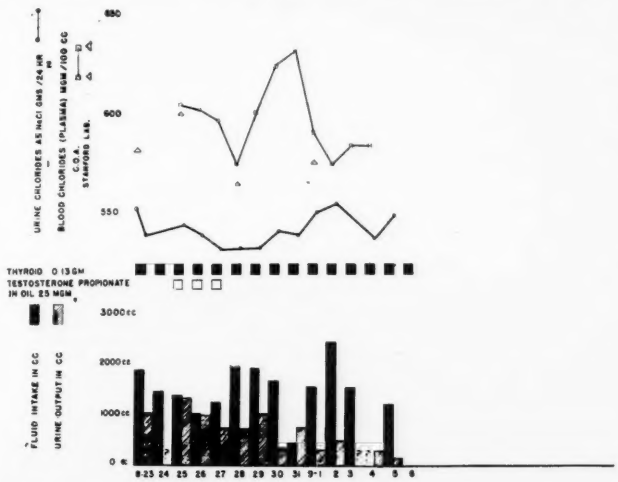


CHART 2. Mrs. T. O'L. Graph showing laboratory data before, during and after testosterone administration for comparison with Mr. F. LaM. (Reprinted by permission of the Stanford Alumni Medical Bulletin.)

was rather lethargic but more active than on his previous admission; the pigmentation of the skin and mucous membranes had not changed. The blood pressures taken during his hospital stay averaged 110/80 and on entry the patient's blood urea was 30 mg. per 100 cc.; blood sugar, 108 mg. per 100 cc.; and serum protein, 6.8 gm. per 100 cc. The red-cell count was 4 million, with 70% (12 gm.) of hemoglobin; the packed cell volume was 31 per cent. The BMR was −29 per cent. A skiagram showed no changes in the sella turcica. An insulin-tolerance test was carried out by the method of Fraser, Albright, and Smith (28) using one-half the intravenous dose of insulin computed from the patient's weight. In spite of this precaution Glycosuria increased steadily out of proportion to the increase in caloric intake and did not return to normal until 3 days after testosterone was stopped. Four days later an attempt was made to control the glycosuria without the daily dose of 2 units of crystalline insulin which had been continued since entry. Glycosuria increased rapidly and the patient was returned to his usual dose of insulin within 3 days. He was discharged 2 days later.

The laboratory data accumulated during the preparation and the experimental period are shown in Chart 1 and Table 1. Normal numbers of active sperm were found in specimens before and after testosterone. A blood assay for gonadotropic hormone was reported

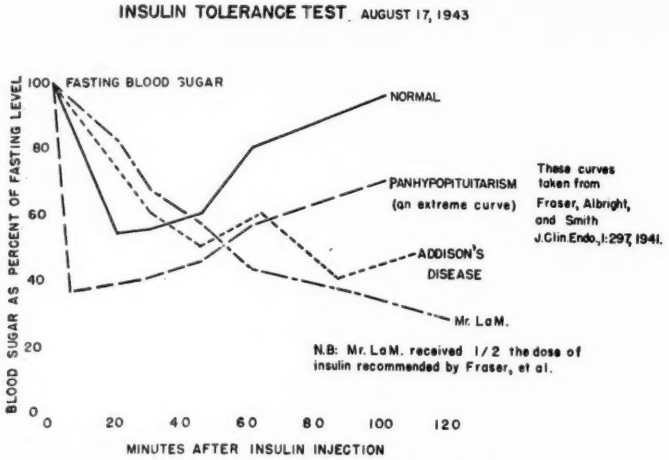


FIG. 1. Mr. F. LaM. Insulin Tolerance Test, August 17, 1943.

the test had to be terminated at 2 hours because of a severe hypoglycemic reaction. The results of the test are shown in Fig. 1 and comparison is made between this curve and that of a normal, of patients with Addison's disease and that of one of the more striking cases of panhypopituitarism cited by Fraser et al. (28). The fasting blood sugar was 166.6 mg. per 100 cc.; 20 minutes after insulin (3 units crystalline), 136.9 mg. per 100 cc.; 30 minutes, 112.3 mg.; 45 minutes, 92.5 mg.; 1 hour, 71.4 mg.; 1½ hours, 60.6 mg.; and 2 hours, 46.5 mg. per 100 cc.

For two weeks of preparation a diet of CHO 225, P 70, and F 50, without added salt; NaCl 6 gm.; percortin 0.4 cc. (2 mg.); and thyroid 0.032 gm. a day were given. The patient then received 25 mg. testosterone propionate in oil intramuscularly on each of 3 successive days. During this period the patient exhibited a remarkable increase in vigor and feeling of well being. His daily caloric intake, which had averaged 1100 calories during the previous week, reached levels of 1500, 1200, and 1600 calories on the first, second, and third days of testosterone administration and returned to its previous level one day later. by Dr. C. F. Fluhmann as showing a normal or slightly increased amount.

DISCUSSION

A careful follow-up of 5½ years has given us an unprecedented opportunity to study the endocrine complexities of this patient. Since the previous report (26), the principal change has been a progressive hypothyroidism. The repeated normal skull plates, the insulin tolerance test, the normal sperm counts, the normal gonadotropic hormone assay and the early history of the case are not in favor of a diagnosis of panhypopituitarism although they do not exclude it (29).

The striking retention of urinary chlorides by testosterone in this case, by comparison with the retention obtained in the control case with functioning adrenals, indicates that in-

TABLE 1. MR. F. LA M. LABORATORY DATA FOR HOSPITAL ENTRY 1943

Date	Fluid Intake	Urine Output	Urine Chloride	P.C.V.[1]	Blood Urea	Sugar	Plasma Chloride	Protein	B.M.R.	Weight	Urine sugar
	cc.	*cc.*	*gm./24 hr.*		*mg.%*	*mg.%*	*mg.%*		%	*kg.*	*gm./24 hr.*
8/ 9				32				6.8		56.5	0.0
8/10	1120	1020	2.95		**30**[2]	**108.1**	**550**		−32		1.7
8/11	1810	1570	4.5							54.2	0.8
8/12	1050	450	1.05							55.1	0.25
8/13	1430	1202	3.48							55.1	0.0
8/14	1550	785	2.29							56.4	0.0
8/15	1770	1160	3.39							55.6	0.0
8/16	1220	2165	6.26							55.7	0.0
8/17	1320	655	1.85							55.6	0.0
8/18	1940	1535	4.44							55.2	0.0
8/19	2180	1465	4.24							55.4	0.0
8/20	1150	1160	3.39							54.0	0.0
8/21	1800	1885	4.08			(100 cc. 50% glucose i.v.)				55.1	21.27
8/22	2220	615	1.77							53.9	0.44
8/23	1430	1215	3.41		**16.5**	**105.2**	**590**			54.5	0.0
8/24	1210	1410	4.12	31				6.05		54.4	0.0
8/25	1850	945	2.76	33			584.5	5.95		54.6	0.92
					Testosterone propionate 25 mg. intramuscular						
8/26	1650	2000	0.59				514.2			54.6	22.06
					Testosterone propionate 25 mg. intramuscular						
8/27	2210	2575	0.71	32			524.2	6.5		53.8	55.83
					Testosterone propionate 25 mg. intramuscular						
8/28	1860	975	0.23		**22**	**322.5**	**546**	6.25	−34.9		36.75
							535				
8/29	1860	990	2.89				528			52.9	23.55
8/30	1750	1115	2.67	30			541.2	5.8		53.5	0.0
8/31	1360	1155	3.2	27	**27**		**610**		−32		
							566				
9/ 1	1150	1175	3.49	30.5			533			54.8	0.0
9/ 2	2590	1820	5.16				513			54.9	15.3
					Crystalline insulin reduced from 2 units to none						
9/ 3	1300	1565	4.54	31			**554**			54.6	34.09
							549.7				
					No insulin						
9/ 4	1050	1615	4.34				513			53.9	43.98
					Crystalline insulin 1 unit						
9/ 5	1260	590	1.67							53.6	0.1
					Returned to regular dose of 2 units crystalline insulin daily						
9/ 6	800	830	2.46	31			538.4			53.4	0.0
					Discharged from hospital						
9/ 7							**576**			53.5	
							543.4				

[1] P.C.V.—packed cell volume (normal for men −45).
[2] Values in bold-face type were obtained by Stanford Laboratory, the others by the author.

tact adrenals are not necessary or stimulating to the action of testosterone, a conclusion in accord with other studies (4, 22, 23). Plasma chloride values fell at the beginning of testosterone administration and returned to normal 4 days after its discontinuance, suggesting that chlorides were concentrated in the tissues during the period of injection.

Remarkable in this patient was the upset of diabetic control with resulting glycosuria, increased glycemia, and increase in urine output. The daily caloric intake rose on the first day of testosterone, fell almost to its previous level on the second day and rose again on the third day; whereas glycosuria increased continuously during the administration of testosterone. The failure of glycosuria to parallel caloric intake and the absence of glycosuria with similar caloric intake before and after the experimental period (8–12 and 8–31 in Chart 1) indicate that glycosuria resulted more from testosterone administration than from increased ingestion of food. Such a lessening of glucose tolerance would be supported by the findings of McCullagh's group (16, 17, 18), but the carbohydrate metabolism was unchanged in the case reported by Talbot et al. (23). Our findings certainly do not indicate the inhibition of gluconeogenesis by testosterone. It seems likely that the inhibition of gluconeogenesis by testosterone described in patients with Cushing's disease may be secondary to the increased use of protein elsewhere rather than a direct interference in the change of protein to carbohydrate in the liver. The negative water balance occasioned by the administration of testosterone in this patient is unique and is probably associated with the loss of diabetic control.

From the therapeutic point of view this patient, who was maintained on carefully established optimum doses of salt, desoxycorticosterone acetate, thyroid and insulin, felt better and improved in activity and appetite during the exhibition of testosterone. The usefulness of testosterone as a supplementary medicament in the treatment of Addison's disease, that has been suggested by other workers (23), must be confirmed or disproved by further investigations.

SUMMARY

1. Some details are given of a $5\frac{1}{2}$ year follow-up of a patient with Addison's disease and diabetes. The most striking change has been a progressive hypothyroidism.

2. The results of testosterone propionate administration in this patient after a control period are compared with results in a patient with intact adrenals. Intact adrenals are not necessary for the action of testosterone.

3. In this patient the administration of testosterone was followed by increased glycosuria and increased appetite, activity, and general feeling of well-being.

REFERENCES

1. AUB, J. C.: Endocrines: the use of testosterone. *N. England J. Med.* 222: 877. 1940.
2. AUB, J. C. AND S. S. KETY: Recent advances in testosterone therapy. *N. England J. Med.* 228: 338. 1943.
3. KENYON, A. T.: Problems in recognition and treatment of testicular insufficiency. *N. England J. Med.* 225: 714. 1941.
4. THORN, G. W. AND G. A. HARROP: The "sodium retaining effect" of the sex hormones. *Science* 86: 40. 1937.
5. THORN, G. W. AND L. L. ENGEL: The effect of sex hormones on the renal excretion of electrolytes. *J. Exper. Med.* 68: 299. 1938.
6. KNOWLTON, K., A. T. KENYON, IRENE SANDIFORD, G. E. LOTWIN AND R. FRICKER: Comparative effects of estradiol benzoate and testosterone propionate in man. *J. Clin. Endocrinol.* 2: 671. 1942.
7. KENYON, A. T., K. KNOWLTON, IRENE SANDIFORD, F. C. KOCH AND G. LOTWIN: A comparative study of the metabolic effects of testosterone propionate in normal men and women and in eunuchoidism. *Endocrinol.* 26: 26. 1940.
8. MCCULLAGH, E. P. AND F. J. MCGURL: Effect of testosterone propionate on epiphyseal closure, sodium and chloride balance, and sperm counts. *Endocrinol.* 26: 377. 1940.
9. EIDELSBERG, J., M. BRUGER AND M. LIPKIN: Some metabolic effects of testosterone implants. *J. Clin. Endocrinol.* 2: 329. 1942.
10. SANDIFORD, IRENE, K. KNOWLTON AND A. T. KENYON: Basal heat production in man and its increase by protracted treatment with testosterone propionate. *J. Clin. Endocrinol.* 1: 931. 1941.
11. MCCULLAGH, E. P. AND H. R. ROSSMILLER: Methyl testosterone: calorigenic activity. *J. Clin. Endocrinol.* 1: 503. 1941.
12. JONES, R., E. P. MCCULLAGH, D. R. MCCULLAGH AND G. W. BUCKALOO: Methyl testosterone; observations on the hypermetabolism induced by methyl testosterone. *J. Clin. Endocrinol.* 1: 656. 1941.
13. MCCULLAGH, E. P. AND R. JONES: Effect of androgens on the blood count of man. *J. Clin. Endocrinol.* 2: 243. 1942.

14. GLASS, S. J.: A case of myxedema with macrocytic anemia successfully treated with thyroid and testosterone. *J. Clin. Endocrinol.* 3: 421. 1943.
15. BASSETT, S. H., E. H. KEUTMANN AND C. D. KOCHAKIAN: Effect of injections of testosterone propionate on a male subject with nephrotic syndrome. *J. Clin. Endocrinol.* 3: 400. 1943.
16. MCCULLAGH, E. P. AND R. JONES: Note on the effect of certain androgens on the red blood cell count and upon glucose tolerance. *Cleveland Clin. Quart.* 8: 79. 1941.
17. LEWIS, L. A. AND E. P. MCCULLAGH: Carbohydrate metabolism of animals treated with methyl testosterone and testosterone propionate. *J. Clin. Endocrinol.* 2: 502. 1942.
18. MCCULLAGH, E. P. AND L. A. LEWIS: Carbohydrate metabolism of patients treated with methyl testosterone. *J. Clin. Endocrinol.* 2: 507. 1942.
19. GAUNT, R., W. O. NELSON AND E. LOOMIS: Cortical hormone-like action of progesterone and non-effect of sex hormones on "water intoxication." *Proc. Soc. Exper. Biol. and Med.* 39: 319. 1938.
20. GREENE, R. R., J. A. WELLS AND A. C. IVY: Progesterone will maintain adrenalectomized rats. *Proc. Soc. Exper. Biol. and Med.* 40: 83. 1939.
21. WERNER, S. C. AND R. WEST: Nitrogen retention, creatinuria, and other effects of the treatment of Simmonds' disease with methyl testosterone. *J. Clin. Investigation* 22: 335. 1943.
22. KENYON, A. T., K. KNOWLTON, IRENE SANDIFORD AND L. FRICKER: Metabolic effects of testosterone propionate in Addison's disease. *J. Clin. Endocrinol.* 3: 131. 1943.
23. TALBOT, N. B., A. M. BUTLER AND E. A. MACLACHLAN: The effect of testosterone and allied compounds on the mineral, nitrogen, and carbohydrate metabolism of a girl with Addison's disease. *J. Clin. Investigation* 22: 583. 1943.
24. THORN, G. W. AND M. CLINTON: Metabolic changes in a patient with Addison's disease following the onset of diabetes mellitus. *J. Clin. Endocrinol.* 3: 335. 1943.
25. NIX, N. W.: Diabetes mellitus associated with Addison's disease. Canad. M. J. 49: 189. 1943.
26. BLOOMFIELD, A. L.: The coincidence of diabetes mellitus and Addison's disease. *Bull. Johns Hopkins Hosp.* 65: 456. 1939.
27. SCHALES, O. AND S. S. SCHALES: A simple and accurate method for the determination of chloride in biological fluids. *J. Biol. Chem.* 140: 879. 1941.
28. FRASER, R., F. ALBRIGHT AND P. H. SMITH: The value of the glucose tolerance test, the insulin tolerance test, and the glucose-insulin tolerance test in the diagnosis of endocrinologic disorders of glucose metabolism. *J. Clin. Endocrinol.* 1: 297. 1941.
29. SALTER, W. T.: Personal communication during a recent visit on which he saw the patient.

Heart Failure in Addison's Disease with Myocardial Changes of Potassium Deficiency

IRVING I. GOODOF, M.D. AND
CYRIL M. MACBRYDE, M.D.

From the Department of Pathology and the Department of Internal Medicine, Washington University School of Medicine, and the Barnes Hospital, St. Louis, Missouri

THE hearts of persons dying of Addison's disease usually show no pathologic change beyond small size and brown atrophy. Clinically, however, it is well recognized that patients suffering with severe adrenal cortical deficiency have very poor cardiac reserve. They suffer dyspnea upon mild exertion. Electrocardiographic evidence of myocardial damage is present in a large percentage of cases (1, 2). In untreated Addison's disease the weakened state of the myocardium may be due to one or more of a number of factors. Among these must be considered: *a*) lack of a specific influence of one or more cortical hormones directly upon the myocardium; *b*) hemo-concentration; *c*) low blood volume and perhaps consequent poor coronary flow; *d*) poor alimentation and exhausted glycogen reserves; and *e*) disturbances in electrolyte balance. The usual circulatory collapse in Addisonian crisis is characterized by extreme dehydration and a falling blood pressure. The changes in electrolytes as reflected in the serum reveal low sodium and chloride and high potassium.

Patients who are very ill with Addison's disease are usually given large amounts of adrenal cortical extract and of sodium chloride and water. In crisis, when the weak myocardium is probably in a precarious state, the sudden addition of a greatly increased load may result in death (3, 4, 5). Desoxycorticosterone, although it represents only a fraction of the desirable activities of the adrenal cortex, is widely employed, since it is the only cortical principle made synthetically and is relatively inexpensive. Injection of this substance has a marked effect upon electrolyte metabolism, causing retention of sodium, chloride and water, and excretion of potassium. In Addison's disease it increases the volume of the blood plasma, corrects the abnormal electrolyte pattern of the plasma and raises the blood pressure. When large amounts are administered, excessive retention of sodium and chloride occurs, the stores of potassium are depleted and the blood volume increases above normal limits. Desoxycorticosterone has only slight effect upon carbohydrate metabolism and upon work performance tests. Overdosage with desoxycorticosterone produces hypertention and circulatory failure (4, 6, 7), a fact now well established.

Before the introduction of desoxycorticosterone in the treatment of adrenal cortical deficiency, it was usually found advisable to give a diet not only rich in sodium, but in which the intake of potassium was restricted. With the use of the new synthetic material, it was found that potassium restriction was dangerous. This apparently resulted from the great increase of potassium excretion produced by desoxycorticosterone. Low blood potassium levels were thus produced, with consequent profound muscular weakness and cerebral effects (3, 8, 9, 10). Cleghorn (11) found that

death from cardiac failure occurred in adrenalectomized dogs maintained on high sodium, low potassium diets.

It is not necessary that animals be adrenalectomized, or that they be given desoxycorticosterone or excessive amounts of salt for the production of cardiac changes. With a diet deficient in potassium but adequate in other respects, Schrader, Prickett and Salmon (12) produced myocardial changes in normal rats. Sykes and Alfredson (13) observed electrocardiographic changes in calves given low potassium diets. In familial periodic paralysis there is low blood potassium during the attacks and Smith (14) has described electrocardiographic changes at such times. By feeding rats a diet extremely low in potassium, but adequate in all other known constituents, necrosis of the cardiac muscle was produced by Follis, Orent-Keiles and McCollum (15). All of the animals which had been on the diet for as long as eight days showed necrosis of the muscle fibers. Such areas then became infiltrated with leukocytes, and proliferation of connective tissue and scarring took place. The potassium content of the heart muscle was 35 per cent lower than that of the normal controls. Darrow and Miller (16) were able to produce the same type of lesion in rats either by moderately excessive doses of desoxycorticosterone or by low potassium diets. The cardiac lesions produced in either instance could be prevented by addition of potassium chloride to the drinking water. Deficit of body potassium was apparently necessary for the production of these lesions.

The importance of potassium in cardiac physiology has been well recognized since the classic studies of Sydney Ringer (17) in 1883. Ringer observed that a sodium chloride perfusate maintained cardiac contractions for only a few beats, with cessation in diastole. The addition of calcium restored the beat for a time, but the heart then came to a standstill in systole. The addition of potassium antagonized the calcium effect; the beat recommenced and was maintained. The three cations, Na^+, K^+, and Ca^{++}, in the same proportions in which they exist in normal plasma, are necessary for normal action of the heart. Functional changes such as those recorded electrocardiographically in man and animals reflect the results one might expect in states of potassium deficiency. The exact mechanism of production of the lesions of the cardiac muscle, however, is obscure. Pathologic changes in the heart muscle of the type produced by potassium deficit might be expected to occur in familial periodic paralysis, or in patients dying with heart failure following excessive desoxycorticosterone therapy. Such, however, have not been described. We here report what we believe to be the first description of the changes in cardiac muscle in a human being dying with potassium deficiency and resultant congestive heart failure.

CASE REPORT

A 21-year-old white single woman was admitted to the Barnes Hospital on September 10, 1942, complaining of weakness, anorexia, and loss of weight. The family history, past history and systemic review were not significant. A year before this admission to the hospital she learned that she had been adopted when an infant and that her true mother was actually a woman whom she intensely disliked. After that time she had been emotionally upset.

The patient had begun to feel fatigued about one year before admission and this fatigue became greatly exaggerated a few months later following a severe sore throat, which was treated with a sulfonamide drug. From this time on, although she continued her school work, she found it difficult to maintain her previous standards. A summer vacation resulted in no alleviation of her symptoms, and the fatigue increased to the extent that eating became difficult. Two weeks before admission to the hospital a diagnosis of hypothyroidism was made and desiccated thyroid was administered. This was discontinued because of vomiting and the patient was sent to Barnes Hospital. There had been a loss of weight of 15–20 pounds since the onset of illness.

On physical examination, the temperature, pulse rate and respiratory rate were normal. There was a slight degree of undernourishment. A generalized brown pigmentation was present, particularly on the exposed surfaces. The blood pressure was 78/50. All tendon reflexes were hypoactive.

The red and white blood cell counts and differential count were normal. The urine was normal. The stomach contained free hydrochloric acid only after histamine. There were 67 mg. of sugar, 31 mg. of nonprotein nitrogen, 440 mg. of sodium chloride and 35.1 mg. of potassium in 100 cc. of blood. The range of normal values for sodium chloride in these laboratories is 580–630 mg. per 100 cc. and for potassium 18–22 mg.

The patient was treated with 100 cc. of Wilson's extract of adrenal cortex, 95 mg. of desoxycorticos-

terone acetate, glucose, and saline over a period of 13 days. Her condition improved promptly. Three cylindrical pellets of desoxycorticosterone acetate, each weighing 75 mg., were implanted subcutaneously and two weeks after admission the blood pressure was normal and she felt well. The blood sodium chloride was now 665 mg. and the potassium level was 17.4 mg. per 100 cc. of plasma and serum, respectively. She was discharged with instructions to take 6 gm. of sodium chloride daily.

Due to a misunderstanding the patient took salt tablets for only two days while at home. She attended classes at school for a few days and then went to bed where she stayed until readmission. During this time her intake of food and fluid was irregular and low. She was brought back to the hospital ten days after discharge, having vomited several times on the day of admission.

On admission to the hospital, the temperature, pulse rate and respiratory rate were again normal. The blood pressure was 105/70. There was extreme lassitude, deeply pigmented skin, dyspnea, and cyanosis of the lips and hands. The superficial lymph nodes were palpable, but were not considered enlarged. There was slight dullness, with suppression of breath sounds at the base of the right lung. Routine laboratory findings were as before. Sodium and potassium determinations were not carried out at this time.

The patient was in the hospital for 6 days on this admission and received a total of 200 cc. of adrenal cortical extract, 5 mg. of desoxycorticosterone acetate, and 7000 cc. of parenteral fluid distributed over the 6 days. The daily urinary output varied from 370–500 cc. There was edema of the lower extremities throughout this terminal period. The patient died on October 21, 1942, apparently in respiratory failure.

Washington University Autopsy No. 10087. The adrenal glands with a small amount of surrounding connective tissue weighed 2 gm. Each gland measured 15 mm. in its greatest dimension, and 1 mm. in thickness. They were gray-white in color and were differentiated from the surrounding tissue only with considerable difficulty. No cortical tissue was seen grossly. The pleural cavities each contained 1500 cc. of clear, pale yellow fluid and 4000 cc. of similar fluid was present in the peritoneal cavity. The heart was slightly enlarged, and weighed 350 gm. It was normal except for the peculiar mottled appearance of the myocardium, which varied between bright red and pale tan in color. The thymus weighed 15 gm. The spleen was large, weighing 375 gm. The malpighian bodies were prominent on the cut surface. The lymph nodes throughout the body were enlarged and firm. The right kidney weighed 35 gm. The lower half was grossly normal. The upper pole was fibrous and contracted. There were two pelves and two complete ureters on the right side, the upper pelvis being thickened and fibrotic. On the left side, the renal pelvis was divided into two parts, each having a separate ureter, which united ten cm. proximal to the urinary bladder.

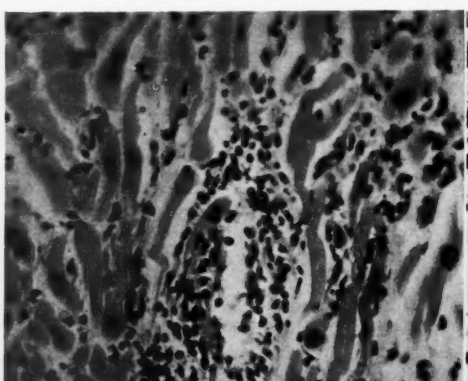


FIG. 1. A focus of necrosis of cardiac muscle with lymphocytic infiltration.

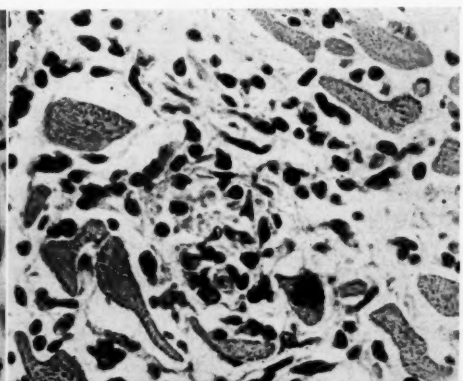


FIG. 2. A minute focus of necrosis of cardiac muscle, involving only one muscle fiber.

Microscopic examination. The adrenal glands contained only a few small islands of large, polygonal, cortical cells with large nuclei. The cells of the medulla were normal.

The lymphoid tissue throughout the body was hyperplastic. The thyroid gland showed the lymphoid hyperplasia most clearly. Large lymphoid follicles were scattered diffusely throughout the gland, which was also diffusely infiltrated with lymphocytes. The acini were small and there was a decrease in the amount of colloid.

The heart was moderately edematous. In many areas there were varying-sized foci of hemorrhage. Throughout the myocardium in the walls of all four chambers there were numerous foci of necrosis of muscle fibers with infiltration of lymphocytes. These foci varied in size from single muscle fibers up to areas 1 to 2 mm. in diameter (fig. 1 and 2).

DISCUSSION

The patient died in cardiac failure and the heart showed changes similar to those previously produced in animals by experimentally induced potassium deficiency. The heart failure was apparent when the patient became weak and nauseated, stayed alone in her room and failed to eat. At this time she discontinued taking sodium chloride and, what is more important, ate practically nothing, but continued to take considerable amounts of fluid. Because of our own experiences and those reported in the literature, we have stressed the importance of an adequate potassium intake (4 to 5 gm. daily) for all patients under treatment with desoxycorticosterone. It seems likely that the presence of the three pellets (75 mg. each) of desoxycorticosterone may have operated only to bring her potassium excretion to a normal level, since there were no signs of cardiac failure when she was having a high sodium intake and a normal potassium intake in the hospital or after leaving the hospital. The actual measured daily absorption from pellets such as this patient was given (cylindrical, 75 mg.) ranges from 0.3 to 0.5 mg. per pellet per day. In the three weeks of preliminary study of this patient it was calculated that her requirement by injection was 2.5 mg. of desoxycorticosterone acetate daily. When given 5.0 mg. every other day intramuscularly she felt reasonably well and her blood pressure ranged from 100/70 to 105/70. It was calculated that 4 pellets would probably be necessary if from 3 to 6 gm. daily of salt was given in addition to that contained in the food. The final decision to use only three pellets was based upon the facts that: (1) the patient was dyspneic and cyanotic when first seen, before treatment was given; (2) there was a suspicion of a small right hydrothorax before therapy; (3) the patient had exhibited some edema during establishment of therapy; (4) it was felt that the signs of pre-existing myocardial damage might be intensified with excessive desoxycorticosterone treatment; and (5) the electrocardiogram before treatment showed myocardial damage.

From the experimental work on animals it is clear that the myocardial changes of potassium deficit may be induced either by increasing the potassium output with desoxycorticosterone or by restricting the intake. In our patient both factors certainly were at work and there is some difficulty in deciding which of the two may have been the more important. There are several reasons why it seems likely that restriction of potassium was the primary factor. (1) This patient received the smallest dose of desoxycorticosterone by pellet implantation which we have ever employed. According to our usual standards, the dose was insufficient. (2) The patient at no time developed hypertension. The blood pressure was always low. In all of our patients who had excessive desoxycorticosterone therapy hypertension has been a constant finding. In those patients developing circulatory failure from excessive hormone therapy as reported in the literature, high blood pressure has also been the rule. (3) The most definite change in this patient's program after leaving the hospital was cessation of food and fluid intake. Failure to take salt and water presumably would not have tended to precipitate circulatory failure, but might have operated in the opposite direction. Restriction of activity because of weakness and nausea should not have diminished but should have improved her cardiac reserve. Potassium restriction, however, in the presence of even the small amount of implanted desoxycorticosterone (which kept the potassium output at approximately normal levels, as shown by previous studies) was disastrous. The rapidity of the change, which must have occurred in the heart muscle as the result of the

deficiency of potassium in the body, fits well with the 8 days observed by Follis, Orent-Keiles and McCollum (15).

SUMMARY

A case of primary atrophy of the adrenal cortices is reported, in which death was caused by cardiac failure. Foci of necrosis of cardiac muscle were present in the walls of all four chambers of the heart. Similar foci have been described in animals which have been given large doses of desoxycorticosterone acetate or which have been fed a diet deficient in potassium. It is believed that such changes may play a part in producing the cardiac abnormalities occasionally seen in patients receiving replacement therapy in Addison's disease.

REFERENCES

1. McGAVACK, T. H.: Some pitfalls in the treatment of Addison's disease. *J. Clin. Endocrinol.* 1: 68. 1941.
2. THORN, G. W., S. S. DORRANCE AND E. DAY: Addison's disease: evaluation of synthetic desoxycorticosterone acetate therapy in 158 patients. *Ann. Int. Med.* 16: 1053. 1942.
3. WILDER, R. M.: Progress in the treatment of Addison's disease. *Proc. Mayo Clin.* 15: 273. 1940.
4. FERREBEE, J. W., C. RAGAN, D. W. ATCHLEY AND R. F. LOEB: Desoxycorticosterone esters: certain effects in treatment of Addison's disease. *J. Am. Med. Assn.* 113: 1725. 1939.
5. THOMPSON, W. O., P. K. THOMPSON, S. G. TAYLOR AND W. S. HOFFMAN: Treatment of Addison's disease with adrenal cortex extract. *Endocrinol.* 24: 774. 1939.
6. McCULLAGH, E. P. AND E. J. RYAN: Use of desoxycorticosterone acetate in Addison's disease. *J. Am. Med. Assn.* 114: 2503. 1940.
7. LEVY-SIMPSON, S., J. F. WILKINSON, H. P. HIMSWORTH, AND A. JONES: Discussion on recent developments in treatment of Addison's disease. *Proc. R. Soc. M. Lond.* 32: 685. 1939.
8. LOEB, R. F., D. W. ATCHLEY, J. W. FERREBEE AND C. RAGAN: Observations on effect of desoxycorticosterone esters and progesterone in patients with Addison's disease. *Tr. Assn. Am. Physicians* 54: 285. 1939.
9. KUHLMAN, D.: Toxic effects of desoxycorticosterone esters in dogs. *Science* 90: 496. 1939.
10. TALBOTT, J. H. AND R. S. SCHWAB: Recent advances in biochemistry and therapeusis of potassium salts. *N. England J. Med.* 222: 585. 1940.
11. CLEGHORN, R. A., C. W. J. ARMSTRONG AND D. C. AUSTEN: Clinical and chemical observations on adrenalectomized dogs maintained by diet high in sodium salts and low in potassium. *Endocrinol.* 25: 888. 1939.
12. SCHRADER, G. A., C. O. PRICKETT AND W. D. SALMON: Symptomatology and pathology of potassium and magnesium deficiences in the rat. *J. Nutrit.* 14: 85. 1937.
13. SYKES, J. F. AND B. V. ALFREDSON: Studies on the bovine electrocardiogram. I. Electrocardiographic changes in calves on low potassium rations. *Proc. Soc. Exp. Biol., & Med.* 43: 575. 1940.
14. SMITH, W. A.: Periodic paralysis: report of 2 fatal cases. *J. Nerv. Ment. Dis.* 90: 210. 1939.
15. FOLLIS, R. H., JR., E. ORENT-KEILES AND E. V. McCOLLUM: The production of cardiac and renal lesions in rats by a diet extremely deficient in potassium. *Am. J. Path.* 18: 29. 1942.
16. DARROW, D. C. AND H. D. MILLER: The production of cardiac lesions by repeated injections of desoxycorticosterone acetate. *J. Clin. Invest.* 21: 601. 1942.
17. RINGER, S.: A further contribution regarding the influence of the different constituents of the blood on the contraction of the heart. *J. Physiol., Lond.* 4: 29. 1883.

COMMUNICATION

FAILURE OF MENOPAUSAL URINE CONCENTRATES TO INDUCE EGG EXTRUSION IN FEMALE XENOPUS FROG TEST FOR PREGNANCY*

RANDALL, Magath and Pansch,[1] Feresten,[2] Heiberg,[3] and Mills[4] have each reported positive Friedman tests (rabbit) for pregnancy with the urine of women in the menopause who were not pregnant. The commonly accepted explanation for this reaction is the finding of increased amounts of follicle-stimulating factor of the gonadotropic hormones in the urine of women going through the climacteric.

These investigations with the rabbit prompted us to study the oviposition response of the South African Clawed Frog (*Xenopus laevis*) to urine from women at or near the menopause. In addition to pure scientific curiosity, the interest in this new frog test for pregnancy with respect to the action of menopausal urine was also stimulated by our previous experimental findings.[5,6] We had earlier shown, in the course of our investigations with *Xenopus laevis*,[7] that the physiologic basis of the egg extrusion phenomenon in the female South African Frog was founded chiefly upon the action of the luteinizing factor of the gonadotropic hormones. This fraction of the gonadotropic hormones is found in excessive amounts in the urine of pregnant women thus serving as the active agent in the test for pregnancy.

The close relationship between the luteinizing factor of pregnancy urine and *Xenopus* oviposition, coupled with the high degree of accuracy of the frog test for pregnancy (99 per cent), prompted this report. Accordingly, we surveyed our series of pregnancy tests and closely analyzed the results obtained with menopausal urines on *Xenopus*.

PROCEDURE

Urine samples from 86 women who had missed one or more periods and who were over 40 years old were studied. Whether the amenorrhea was due to pregnancy or to the onset of the menopause was unknown. Upon test all the patients were found to be in the early menopausal state. All tests on the *Xenopus* frogs were made according to our established technic,[8] using two mature female *Xenopus* for each test and subjecting each animal to a one cubic centimeter injection of concentrate equivalent to forty cubic centimeters of whole urine. Any extrusion of eggs within six to twelve hours after injections is indicative of a positive reaction.

Not one of all the eighty-six urine samples tested was able to induce external oviposition in the *Xenopus*. Each case was reported as negative for pregnancy and negative for increase in gonadotropic hormones.

DISCUSSION

From the above findings it is apparent that menopausal urine does not stimulate ovulation and egg extrusion in *Xenopus*. This lack of response may be explained by the paucity of gonadotropic luteinizing-factor in such urine, while the phenomenal response of the South African Frogs to the urine of pregnancy can be attributed to the presence of a marked increase of this gonad-stimulating fraction. Our earlier experimental reports substantiate this explanation. The variation in response of the South African Frogs to the separate gonadotropic factors, being stimulated by the luteinizing factor and unaffected by the follicle-stimulating factor, should serve to enhance the value of this test animal in differentiating pregnancy from menopause.

* Aided by a grant from the New York Biologic Research Foundation, New York, N. Y.

[1] Randall, L. M., T. B. Magath and F. N. Pansch: A study of "false" Friedman tests for pregnancy. *J. Am. Med. Assn.*, 114: 471. 1940.

[2] Feresten, M.: Report of 1600 Aschheim-Zondek tests (Friedman modification). *Endocrinol.* 21: 116. 1937.

[3] Heiberg, B.: Report of Friedman test as pregnancy reaction. *Ugesk. f. laeger.* 99: 387. 1937.

[4] Mills, H. R.: Friedman test for pregnancy; report of 213 cases. *J. Florida Med. Assn.*, 22: 11. 1935.

[5] Weisman, A. I., and C. W. Coates: The frog test (*Xenopus laevis*) as a rapid diagnostic test for early pregnancy. *Endocrinol.* 28: 141. 1941.

[6] Weisman, A. I. and C. W. Coates: Use of the South African Clawed Frog (*Xenopus*) as an assay animal for gonadotropic hormones. *J. Lab. & Clin. Med.* 28: 1631. 1943.

[7] Weisman, A. I., A. F. Snyder and C. W. Coates: Physiology of egg extrusion in female *Xenopus* test for pregnancy. *Endocrinol.* 31: 323. 1942.

[8] Weisman, A. I., A. F. Snyder and C. W. Coates: The frog test (*Xenopus laevis*) as a rapid diagnostic test for pregnancy. *Am. J. Obst. & Gynec.* 43: 135. 1942.

SUMMARY

Urine concentrates of 86 women who had missed one or more menstrual periods and who were passing through the early phases of the climacteric were tested on *Xenopus* frogs. No egg-extrusion response was found in the case of any patient tested. The use of this test animal in differentiating pregnancy from early menopause is suggested.

ABNER I. WEISMAN
CHRISTOPHER W. COATES
From the Department of Gynecology, Jewish Memorial Hospital, and New York Zoological Society, New York, N. Y.

LETTER

NOMENCLATURE OF PITUITARY PRINCIPLES

TO THE EDITOR

I am moved to write you after reading the editorial article in the December issue of *Endocrinology* by Dr. George W. Corner, Sr. on the matter of nomenclature of those pituitary principles which effect other endocrine glands. I have preferred, in the past, to use the term "gonadotropin" rather than the slightly longer form with the "h" inserted. I must confess that Dr. Corner's reasoning has persuaded me to a change in order to be more reasonable, more accurate and also to be in step with many of our colleagues, especially in Great Britain and in Canada. By way of adding my personal endorsement, I have decided that henceforth the Yearbook of Endocrinology which appears under my editorship will carry all of the pituitary principles with the suffix "trophin" and this will appear in that form beginning in the 1943 issue which is now in press. I propose to make this true in personal publications.

I have been assured that there is a high probability that the Council on Pharmacy and Chemistry of the American Medical Association, and the Committee on Revision of the United States Pharmacopoiea will take similar action. If so, this would add very significantly to the unanimity on this matter. May I suggest therefore that the editorial staff of the *Journal of Clinical Endocrinology* give serious consideration to making this change and asking authors to adopt the new spelling.

ELMER C. SEVRINGHAUS
State of Wisconsin General Hospital Madison 6, Wisconsin

ASSOCIATION NOTICE

ANNOUNCEMENT OF THE ANNUAL MEETING

The Twenty-Seventh Annual Meeting of The Association for the Study of Internal Secretions will be held in Chicago, Illinois, on Monday, June 12, 1944, and if sufficient papers of merit are available the Meeting will be extended to two days, June 12 and 13. The Stevens Hotel will be the headquarters for registration and for the scientific and business sessions. Room reservations should be made directly with the Stevens Hotel. Hotel and transportation reservations should be made immediately.

The Chairman of the Local Committee is Dr. Willard O. Thompson, 700 North Michigan Avenue, Chicago.

PRESENTATION OF PAPERS

1. The title of the paper and four copies of a comprehensive abstract should reach the President, Dr. E. Kost Shelton, 921 Westwood Boulevard, Los Angeles, California, not later than Apr. 10, 1944.

Abstracts submitted should be in proper form for printing in the program. Not more than the first 200 words can be included in the printed abstract.

2. Non-members who wish to present papers must have their titles and abstracts introduced by members.

3. The abstracts of papers will be considered by the Program Committee and the final program announced about May 10, 1944.

4. Papers will be limited to ten minutes for presentation. A ten-minute presentation is designed for condensed discussion of new investigations, either in laboratory or clinical phases of endocrinology. Previous publication or presentation before other societies of national membership may be cause for omitting a paper from the program.

5. Papers presented at the Annual Meeting may be submitted for publication to the Editor of *Endocrinology* or *The Journal of Clinical Endocrinology*. Such submission is invited. Acceptance of a paper for the program does not necessarily mean its acceptance for publication.

You are invited to bring this announcement to the attention of your colleagues and associates who have endocrine research in progress.

NOMINATION OF OFFICERS

The By-Laws of the Association provide that nominations for all elective offices shall be made by a Nominating Committee and forwarded to the Secretary at least sixty days before the annual meeting. The Nominating Committee for the current year, appointed by the President and accepted by the Council, is as follows:

Dr. E. Perry McCullagh (Chairman), Cleveland Clinic, Cleveland, Ohio.
Dr. C. N. H. Long, Yale University School of Medicine, New Haven, Connecticut.
Dr. Warren O. Nelson, Department of Anatomy, Wayne University, Detroit, Michigan.

The By-Laws also provide (Article V, Section 2) that "Any member of the Association may submit nominations to the Nominating Committee for its consideration." Nominations may be sent to the Chairman, Dr. E. Perry McCullagh, before Apr. 10, 1944.

The terms of the following officers expire at the time of the Annual Meeting in Chicago in 1944:

President-Elect	Carl R. Moore
Vice-President	John C. Burch
Secretary-Treasurer	Henry H. Turner

Council Members

P. E Smith	George W. Thorn
M. A. Goldzieher	Edgar Allen (deceased)
	(Term expires 1946)

Publication Board

E. C. Hamblen	Carl R. Moore

AWARDS

The E. R. Squibb & Sons Award

The E. R. Squibb & Sons Award of $1000 was established in 1939, and was given first in 1940 to Dr. George W. Corner, in 1941 to Dr. Philip E. Smith, and in 1942 to Dr. Fred C. Koch. A special Committee of five members of the Association chooses an investigator or investigators in the United States or Canada for one of the best contributions to endocrinology.

The Ciba Award

The Ciba Award to recognize the meritorious accomplishment of an investigator not more than 35 years of age in the field of endocrinology was established in 1942, but no recipient was selected due to lack of time. The work cited may be either in the field of pre-clinical or clinical endocrinology. The Award is for $1200. If the recipient should choose to use the Award toward further study in a laboratory other than that in which he is at present working, the Award will be increased to $1800. The option is left entirely to the recipient.

Each member has the privilege of making one nomination for each Award. A nomination should be accompanied by a statement of the importance of the nominee's contributions in endocrinology and by a bibliography of the nominee's most important publications, and reprints if possible. Five copies should be sent to the Secretary, Dr. Henry H. Turner, 1200 North Walker Street, Oklahoma City, Oklahoma, not later than March 20, 1944.

E. Kost Shelton, President
Henry H. Turner, Secretary

Abstracts of CURRENT ENDOCRINE LITERATURE

Editor: DANIEL A. MCGINTY. *Collaborators:* ISRAEL BRAM, JOHN C. DONALDSON, J. W. EVERETT, MURRAY B. GORDON, R. B. GREENBLATT, E. C. HAMBLEN, HANS O. HATERIUS, CHARLES W. HOOKER, R. G. HOSKINS, J. E. HOWARD, J. T. LEWIS, T. H. MCGAVACK, A. E. MEYER, MARY L. MILLER, C. C. PFEIFFER, DORIS PHELPS, J. P. PRATT, E. C. REIFENSTEIN, JR., BORIS B. RUBENSTEIN, PATRICIA H. SMITH, RUTH ST. JOHN, CHALRES W. TURNER, EMMERICH VON HAAM, HAROLD WOOSTER.

BOOK REVIEW

SNAPPER, I.

Medical clinics on bone diseases. A text and atlas, Interscience Publishers, New York, 1943.

This monograph deals with certain aspects of osteitis fibrosa cystica (hyperparathyroidism, v. Recklinghausen's disease), osteomalacia, osteitis deformans (Paget's disease), multiple myeloma, Gaucher's disease, osteitis fibrosa disseminata, and lipoid granulomatosis. The discussion is built about case reports illustrated by excellent photographs, and supplemented by a partial review of the literature. The author was formerly Professor of Medicine in Peiping Union Medical College, Peiping, China.

More than half of the work is devoted to conditions associated with hyperfunction of the parathyroid glands, both primary and secondary. Among other topics, the observations of von Recklinghausen, classical osteitis fibrosa cystica with gross bone involvement, renal complications of hyperparathyroidism with and without involvement of the skeleton, muscular and gastrointestinal symptoms from hypercalcemia, differential diagnosis of hyperparathyroidism, parathyroidectomy and post-operative complications are discussed. The author gives little discussion of the importance of calcium and phosphorus in the diet in preventing bone disease in hyperparathyroidism, and he is reluctant to admit the existence of cases in which the only demonstrable pathology is in the renal system.

Parathyroidism secondary to osteomalacia and chronic renal insufficiency are discussed. Particular attention is given to the histological picture of the bone lesions in these conditions. The role of the acidosis in producing these bone lesions, and the effect of the secondary hyperplasia of the parathyroids in altering the chemistry of the blood are not made clear by the author. He believes that hypophosphatemia in some of the cases is due to osteomalacia from poor diet and lack of sunlight rather than hyperparathyroidism; he does not discuss the effect of overcoming the acidosis on the bone lesions or on the disturbed blood chemistry; he does not mention that hypocalcemia may result from the excretion in the urine of calcium as a fixed base to combat the acidosis.

The author describes osteomalacia and rickets as it is found in China where poor diet and lack of exposure to sunlight combine to produce avitaminosis D. Adult osteomalacia in the United States is seen commonly as a result of steatorrhea from such disorders as non-tropical sprue or pancreatic disease; these conditions are not discussed. Sections are devoted to osteitis deformans and its differential diagnosis from osteitis fibrosa cystica, to Gaucher's disease, and to multiple myeloma and its possible connection with leukemia. A detailed discussion is given of lipoid granulomatosis and xanthomatosis of the bone. The author contends at some length that osteitis fibrosa disseminata (Albright) or multiple fibrous dysplasia (Lichtenstein) are manifestations of lipoid granulomatosis. His chief argument is that the bone biopsy in these conditions must always be performed on a fresh lesion as the xanthoma tissue has disappeared and been replaced by fibrous tissues in the older lesions.

In the differential diagnosis of hyperparathyroidism, the author considers Paget's disease, multiple myeloma, generalized cancer metastases in bone, decalcification of bone in hyperthyroidism, lipoid granulomatosis of bone or xanthomatosis ossium (including osteitis fibrosa disseminata (vide supra), chronic renal insufficiency and osteomalacia. There is no discussion of sacroidosis, lymphoma involving bone, benign metastasizing hemangioma, or osteoporosis. The most

surprising omission is osteoporosis, which is being recognized as one of the most common metabolic bone disorders; post-menopausal osteoporosis, in particular, has been widely observed. It is regretted that the author did not include his analysis of neurofibromatosis involving bone, osteopetrosis, the effect of lead and fluoride on bones, hypoparathyroidism from other causes than parathyroidectomy, the effect of vitamin D on calcium and phosphorus metabolism, and the various conditions causing tetany.

While the general discussion is excellent, the interpretations given to some of the investigations quoted from the literature are misleading and tend to undermine confidence in the rest of the work. Also, the author is not as precise as is desirable: he speaks of normal calcium and phosphorus metabolism when he means normal levels of calcium and phosphorus in the blood. In spite of these criticisms, the monograph is a valuable contribution in a field largely unknown to most physicians. It should find considerable use as a reference work among persons interested in these disorders. The author and publishers are to be commended on the mechanical features of the book. There are 225 pages, 30 plates, 38 tables, an extensive bibliography at the end of each section, an author and a subject index.—*E.C.R., Jr.*

ADRENALS

BOURQUE, J. E., H. O. HATERIUS, AND ELIZABETH GLASSCO

Treatment of circulatory collapse of experimental venous occulusion: Use of adrenal cortical extract and saline solution. *Proc. Soc. Exp. Biol. & Med.* 52: 313. 1943.

The shocklike syndrome of circulatory collapse and prostration was induced in a series of 18 dogs by a regional venous occlusion. Treatment at the time of collapse, by infusion of adrenal cortical extract (Eschatin) and physiological saline, resulted in a marked increase in survival time in 6. In a control group of 12 dogs, saline infusion alone prolonged survival time in 2. Adrenal cortical extract alone in a series of 12 proved ineffective.—*C.W.T.*

GAUNT, R.

Protection of normal rats against death from water intoxication with adrenal cortical substances. *Proc. Soc. Exp. Biol. & Med.*, 54: 19. 1943.

Large doses of adrenal cortical extract or desoxycorticosterone acetate were observed to protect normal rats from doses of water which otherwise produced lethal water intoxication.—*C.W.T.*

GRAHAM, J. S.

Effect of carbon arc irradiation and adrenal cortical preparations on capillary permeability. *Proc. Soc. Exp. Biol. & Med.*, 54: 101. 1943.

The exposure of the abdomen of rabbits to the carbon arc lamp for 30 to 40 minutes at a distance of one meter followed by the intravenous injection of the dye trypan blue produced an extreme blue coloration of the skin and viscera many times more marked than that of the controls. When 10 mg. of desoxycorticosterone acetate or 5 cc. of cortin was injected intramuscularly at the time of irradiation or before, the tissues of these animals were comparable to the control group. These observations are taken to indicate that the adrenal cortical hormones are capable, under these conditions, of preventing the increased permeability occurring in the minute vessels by the action of substances released from tissue undergoing inflammatory changes.—*C.W.T.*

LAPIN, J. H., S. F. GOLDMAN AND A. GOLDMAN

The clinical use of adrenal cortical hormone. *N. Y. State Jour. Med.* 43: 1964. 1943.

Upon the basis of personal experiences, the authors advise therapy with desoxycorticosterone acetate and adrenal cortical extract in the following conditions.

1. Hypo-adrenal syndromes—Addison's disease, sub-clinical hypoadrenalism (weakness, loss of weight and hypotension) and secondary glandular hypofunctions. 2. Hypoglycemia. 3. Hypothyroidism. 4. Medical shock syndromes. 5. Disturbances of water metabolism and electrolyte concentration, where they would be benefited by the prevention of loss of water, sodium and chloride through the urine, deserve a trial of cortate therapy. Investigations should be carried out with cortate therapy to note if an increased intestinal resorption of water and salts results in such conditions as alimentary toxicosis of infancy with diarrhea and dehydration, ulcerative colitis and perhaps dysentery and typhoid. Hyperemesis gravidorum seems to be benefited. 6. Polyglandular syndromes are probably affected by cortate therapy—the gonads are notably influenced. The dangers of adrenal cortical extract and desoxycorticosterone are discussed. Overdosage of the sodium factor may be obviated by

carefully watching the urinary volume, signs of edema, acceleration of the pulse and rise in blood pressure. Overdosage of carbohydrate metabolism has not been noted in the literature, but a constant supply of glucose and frequent carbohydrate tolerance tests are undoubtedly wise precautions. Inhibition of the immature rat ovary and atrophy of the testis have been reported following ingestion of large doses of cortate. Temporary inhbitions of adrenal cortical function following therapeutic doses of adrenal cortical extract and "compensatory atrophy" after the administration of large doses have been noted by some investigators.—*M.B.G.*

RHOADES, J. E., W. A. WOLFF, H. SALTONSTALL AND W. E. LEE

Further experiences with adrenal cortical extract in the treatment of burn shock. *Ann. Surg.* 118: 982. 1943.

Twelve patients with extensive superficial burns were treated with adrenal cortical extract in doses comparable to those recommended in the treatment of addisonian crisis. The ability of these patients to retain plasma given by transfusion was compared with that of 13 control patients who received no extract. The local treatment consisted in tanning all areas except hands and face and genitalia by one of the commonly used agents. Plasma was administered between the 12th and 30th hours after the burn and the new increment in circulating plasma between the 12th and 36th hours compared with the amount of plasma administered. The mean per cent retention for the treated series was 57% as compared with 57% for the control series. In terms of grams of circulating plasma protein the mean per cent retention for the treated series was 46% as compared with 57% for the control series. It was concluded that the results did not indicate that adrenal cortical extract, in the doses used, is of value for routine use in the management of burn shock.—*D.P.*

SCHWEIZER, M., A. EHRENBERG AND R. GAUNT

Effects of adrenal and thyroid hormones on water exchange in hypophysectomized rats. *Proc. Soc. Exp. Biol. & Med.* 52: 349. 1943.

The effects of adrenal cortical and thyroid substances were studied on the water exchange and related phenomena in hypophysectomized rats during periods after the initial high post-operative diabetes insipidus had subsided. Desoxycorticosterone acetate in one mg. daily doses elevated water exchange but not to levels characteristic of diabetes insipidus, whereas whole extract of the adrenal cortex was without effect. Thyroid-feeding in doses that restored oxygen consumption at least to normal, elevated the water intake slightly but not the urine output. There was an associated rise in urine specific gravity. The diuretic effects of thyroid hormone under other circumstances in the rat must depend upon the presence of an anterior pituitary. Non-toxic doses of thyroxine, although affecting oxygen consumption, had no effect on water exchange. When desoxycorticosterone and the larger doses of thyroid were given in combination, the toxicity of the latter was overcome. Water intake was doubled, but urine volume did not increase proportionately due to the opposing action of the thyroid substance.—*C.W.T.*

ENDOCRINE GENERAL

BURCH, J. C., AND DORIS PHELPS

An experimental approach to the problem of menstrual disorders. *Ann. Surg.* 116: 604. 1942.

In previous publications, the authors have presented a concept of the etiology of functional menstrual disorders which may be stated as follows. These disorders result from an ovarian failure. The ovarian failure may be primary, due to inherent ovarian disease, or secondary, due to extra-ovarian causes, such as pituitary, thyroid or other endocrine disease and various types of constitutional disease. The approximate degree of ovarian involvement is indicated by the endometrium. There is no constant correlation between the primary lesion, the menstrual symptoms and the endometrial reaction. In the present communication, the experimental evidence supporting the above concept is summarized, the various phases of the problem of abnormal menstruation are discussed and observations on endometrial vascular phenomena associated with abnormal uterine bleeding are described briefly. By combined treatment with estrogen and progesterone, menorrhagia was produced in castrated rhesus monkeys bearing intraocular endometrial transplants. As observed in the transplants, the endometrial vascular phenomena characteristic of the abnormal bleeding were essentially similar to those characteristic of normal menstruation except that the interval between initial bleeding and restoration of the circulation was prolonged as compared with normal menstruation.—*D.P.*

THYROID

MACKENZIE, J. B., AND C. G. MACKENZIE

Production of pulmonary edema by thiourea in the rat, and its relation to age. *Proc. Soc. Exp. Biol. & Med.* 54: 34. 1943.

Thiourea, a compound which has recently been shown to relieve thyrotoxicosis in man through its action in preventing thyroxine synthesis in the thyroid gland, has been observed to produce rapid and fatal pulmonary edema in adult rats. The immature rat is much less susceptible to the pulmonary edema tolerating 50 times the lethal dose for the adult. The toxic dose is roughly 10 times the effective dose for thyroid inhibition in this animal.—*C.W.T.*

MACKENZIE, C. G. AND JULIA B. MACKENZIE.

Effect of sulfonamides and thioureas on the thyroid gland and basal metabolism. *Endocrin.* 32: 185. 1943.

Hyperemia and enlargement of the thyroid gland has been produced in rats, mice and dogs by the administration of sulfonamides and thioureas. Histologically, there is a reduction in colloid and an increase in the height of the thyroid epithelium. Thyroidectomy cells are found in the pituitary. The reaction does not occur in the chick or the guinea pig. In immature rats receiving from 0.5 to 3.0 per cent of dietary sulfaguanidine (free sulfaguanidine in the blood, 1.75 to 14.6 mg. per cent) the thyroid weight at the end of 2 weeks was proportional to the dietary level (roughly proportional to the blood level) and represented an increase in weight of 60 to 350 per cent. Two per cent sulfaguanidine (free sulfaguanidine in the blood 8.6 mg. per cent) produces in 2 days an increase in thyroid weight of 35 per cent. The increase in size using this dietary level of the drug was, during 55 days, a logarithmic function of the time. Sulfanilamide was less active than sulfaguanidine, sulfadiazine or sulfapyridine in producing thyroid enlargement. Thiourea was approximately 8 times more effective than the same dietary level of sulfaguanidine during a 2-week-test period. Diethylthiourea and allylthiourea were also active while acetylthiourea and thioacetamide were negative under the same conditions. The rate of thyroid weight increase in rats fed a given level of sulfaguanidine decreases with age. The rate of histologic response decreases to a lesser degree. This age difference can only partially be accounted for by a decrease in the blood level of the drug. In sexually mature male rats fed 2 per cent of sulfaguanidine the B.M.R. is −10 at 5 to 7 days and −20 at 10 to 14 davs The thyroid-metabolic effect produced in rats on a stock diet is not prevented by a number of dietary factors including para-aminobenzoic acid, vitamin C and liver. It is not prevented by iodine. This effect is entirely prevented by thyroxin at a dosage level of 1 μg. per 10 gm. of body weight. Hypophysectomy likewise prevents the thyroid alteration resulting from feeding 2 per cent sulfaguanidine to rats. Sulfaguanidine does not further depress the B.M.R. of thyroidectomized rats nor prevent their response to small doses of thyroxin. The thyroid enlarging effect of the sulfonamides and thioureas is probably mediated through the anterior pituitary. That other causative factors may be involved in this effect is not excluded.—*Author's Summary.*

MANN, W., AND C. P. LEBLOND

Chemical transformation of the iodine fixed by the thyroid gland. *So. Surgeon* 11: 828. 1942.

By means of radioactive iodine, the fate of iodine in the thyroid gland was examined in normal animals receiving very small amounts of iodine comparable to the quantities present in the food of man and in animals receiving a fairly large dose of iodine comparable to the amounts administered in medical therapeutics. I. Adult dogs were given 10 cc. of a radioactive iodine solution intravenously and sacrificed at intervals up to 48 hours after the injection. There was a rise in the total quantity of radioactive iodine fixed in the thyroid up to the highest level at 48 hours. Diiodotyrosine was the first compound toappear in the gland and this fraction fulfilled the requirements for a precursor of thyroxine. In the thyroxine fraction the specific radioactivity gradually increased to reach equilibrium toward the 48th hour after injection. It was calculated that 1.55% of the thyroxine was fixed per hour. In the inorganic iodine fraction an equilibrium was reached at about the 8th hour after the injection. II. A dosage of 0.5 mgm. of iodine per 100 gms. body weight was administered to guinea pigs in the form of a short-life isotype. Analysis of the thyroids revealed that a high percentage of the radioactivity fixed therein entered the gland as iodide. These results were checked by use of a long-life isotype in dogs. Following the administration of a dosage of 5 mgm. of iodine per kg. body weight, 70% of the radioactive iodine in the thyroid was in inorganic form, 1% was as thyroxine and the rest was as diiodotyrosine. The

specific radioactivity was maximum in the iodide and higher in the diiodotyrosine than in the thyroxine. The results of the experiments were interpreted as indicating the existence in the thyroid of two mechanisms for the concentration of iodine: (1) by way of rapid formation of diiodotyrosine which predominates when extremely small doses of iodine are given; and (2) by way of a selective uptake of inorganic iodine which predominates when large doses of iodine are given. The following conclusions were drawn. 1. In physiologic conditions the iodide coming from the blood stream accumulates in the thyroid gland mainly as diiodotyrosine. The diiodotyrosine fraction is the natural precursor of thyroxine. The results indicate that 1.55% of the thyroxine contained in the thyroid gland is formed per hour. 2. When excessive doses of iodine comparable to those used in medical practice are administered to an animal, the iodine is incorporated in the gland probably as stored iodine. In relation to the large dose administered, the proportion which is transformed into diiodotyrosine is much smaller than in the case of small dose administration.—*D.P.*

PETERS, J. P., AND E. B. MAN.

The interrelations of serum lipids in normal persons. *J. Clin. Invest.* 22: 707. 1943.

Determinations of total cholesterol, lipid phosphorus, and total fatty acids were made on the sera of a relatively large number of individuals, while less frequent determinations of other lipid constituents were performed. The normal range of any lipid fraction from person to person or in a single individual from time to time was great: from 107 to 320 mgms. per cent for cholesterol; from 6.1 to 14.5 mgms. per cent for lipid phosphorus; and from 0 to 17.8 m. eq. per liter for the fatty acids of free fat. Lipids for obese were comparable to those of normal adults; the same held true in a study of 34 obese and 17 normal children. No distinction could be made between the values for males and those for females. In 103 determinations, the ratio of cholesterol to lipid phosphorus was shown to be more constant than the concentration of either of the components. It was also observed to vary directly with the concentration of cholesterol. In 19 observations, the free cholesterol-total cholesterol ratio averaged 0.28 with a narrow variation from 0.25 to 0.32, even in the face of wide fluctuations for the two fractions concerned. Values for free fat in 102 individuals were found to vary more widely than did either the lipid phosphorus or cholesterol fractions, and in a manner totally independent of them. The authors conclude that the determination of any single lipid constituent, even though often repeated, is not as informative as the correlation of the ratios existing between them.—*T.H.Mc.G.*

PETERS, J. P., AND E. B. MAN.

The interrelations of serum lipids in patients with thyroid disease. *J. Clin. Invest.* 22: 714. 1943.

"The lipids of the serum of a large number of patients with thyroid disease have been analyzed." The observations confirm the generally accepted concept that cholesterol values rise when the thyroid gland is removed and fall when substances with known thyroid activity are given. However, normal concentrations of cholesterol may be found in the serum of patients with hyper- or hypo-thyroidism, as the level to which cholesterol rises or falls is roughly related to the normal cholesterol concentration of the given subject. The ratio of free total cholesterol is unchanged by variations in thyroid activity. The ratio of total cholesterol to lipid phosphorus is the same as that seen in normal subjects only so long as the values for cholesterol remain within the normal range. The ratio diminishes when cholesterol values are low, and rises when they are high. No relation could be demonstrated between the amount of neutral fat in the serum and the height of the cholesterol figure.—*T.H.McG.*

RAWSON, R. W., S. HERTZ AND J. H. MEANS

Thiocyanate goiter in man. *Ann. Int. Med.* 19: 829. 1943.

With the extended use of soy bean in the diet, sulfonamides in infection and thiocyanate in hypertension, it is of practical importance to know whether these agents have any goitrogenic action in man. It has been reported that soy bean flour when fed to rats has a strongly goitrogenic action and that this type of goiter could be prevented by the administration of iodine. Most of the sulfonamides are goitrogenic but it is not possible to prevent this action by means of iodine. Thyroxin, however, does have a prophylactic action.

The authors report the development of goiter in two patients who were receiving potassium thiocyanate for treatment of hypertension. These goiters were associated with decreased thyroid

function as evidenced by symptoms of hypothyroidism, low B.M.R., low blood plasma iodine, decreased urinary excretion of labeled iodine and increased urinary excretion of thyrotropic hormone in the inactivated form, hyperplasia of the thyroid and exophthalmos in one case.

The theory is advanced that this drug blocks the formation of thyroid hormone by the thyroid gland and that the consequent lowering of concentration of active thyroid hormone in the blood stream causes stimulation of the anterior pituitary to produce an excess of thyrotropic hormone. This in turn causes thyroid hyperplasia but, because of the block, no increase in physiologically active thyroid hormone output. It is a hyperplasia of frustration. An excess of administrative iodine may force the block and cause liberation of active hormone. Administration of thyroid by-passes the block and relieves the situation by substitution. Thiocyanate goiter can probably be prevented by prophylactic doses of iodine. It can be relieved by administration of thyroid even when thiocyanate administration is continued in hypertension.—*M.B.G.*

SEVERANCE, A. O., AND SYLVIA JOHNS

The pathologic changes of the thyroid gland. *Texas State J. Med.* 38: 717. 1943.

Of 148 surgical specimens, 6.4% showed malignant tumors, 33% total neoplasms, and 41% were toxic goiters. These findings are given in view of the opinion that there is little toxic thyroid disease in southwest Texas, and that most thyroid disorders there are due to neoplasms. The classification of thyroid disease and differential diagnosis are discussed.—*Courtesy Biol. Absts.*

TIERNEY, N. A., AND J. P. PETERS.

The mode of excretion of creatine and creatine metabolism in thyroid disease. *J. Clin. Invest.* 22: 595. 1943.

The rather difficult measurement of serum creatine was carried out by use of Peters' procedure adapted to the Evelyn-Molloy photoelectric colorimeter. The serum creatine of 12 normal males varied from 0.17 to 0.50 mgm. per cent, and the serum creatinine from 1.05 to 1.65 mgm., while similar determinations in 19 normal women yielded figures ranging from 0.35 to 0.93 in the first instance and from 0.90 to 1.50 in the second. No creatinuria was observed in 22 normal males, while it occurred in 13 of 19 females. In hyperthyroidism, three of eight female patients had markedly elevated serum creatine levels, while the remainder showed high normal values; creatinuria was always present. Two of three hyperthyroid males showed high serum creatine and creatinuria. In all instances, values were within normal limits following iodine therapy. Subsequent to the administration of 1 gram of creatine to normal males and females serum creatine rose rapidly to a peak in 1 hour, returning to the pre-ingestion levels within three hours. In hyperthyroid subjects, the curves were exaggerated and longer sustained, with creatinuria appearing in the male and an exaggeration of normal creatine excretion in the female. Creatine never appeared in the urine in any instance until the concentration in the serum was 0.58 mgm. per cent or more. Serum creatine and creatine clearance showed a roughly straight line relationship when serum creatine was greater than 0.5 mgm. per cent, although scattering of the figures in a small series of cases prohibited the actual plotting of a curve.—*T.H.McG.*

WILENSKY, A. O.

The proper selection of thyrotoxic patients for subtotal thyroidectomy. *M. Rec.* 156: 350. 1943.

The author classifies thyrotoxicosis into 3 groups: exophthalmic goiter, thyrotoxicosis without exophthalmos, and localized adenoma of the thyroid with mild hyperthyroidism. In the absence of complicating factors all of the above cases should undergo subtotal thyroidectomy, with proper pre-operative preparation, which includes rest, a high caloric diet, medical and physical sedation, and treatment with Lugol's solution. If the patients do not respond to Lugol's solution within 12 to 14 days, they should be immediately operated on anyway. In the presence of cardiac disease, selection of time of operation is difficult, and primary attention should be paid to improving the cardiac disability. Without marked improvement, operation should be rejected. In diabetic conditions operation is postponed until the hyperglycemia and glycosuria are corrected. When nasal accessory sinus disease with postnasal drip is found, operation without rhinological correction may result in postoperative pyrexia. Medical treatment should be chosen exclusively in the presence of any complications which indicate that the operation may result fatally. One improves or "cures" the condition by medical means, and holds the improvement by surgery.—*H.W.*

WILLIAMS, R. H. AND G. W. BISSELL.

Thiouracil in the treatment of thyrotoxicosis. *New England Jour. Med.* 229: 97. 1943.

Nine unselected cases of thyrotoxicosis have been treated with thiouracil in initial doses of .2 gram five or six times daily. With moderate clinical improvement and fall in metabolic rate, medication is reduced to .2 gram three or four times daily. Dosage is further reduced to .2 gram once or twice daily when the metabolic rate is normal. In all of the nine cases studied, toxic manifestations disappeared and the basal metabolic rate returned to a normal range. Blood iodine studies, conducted on 4 patients, showed in each case a fall of the protein-bound iodine to a low normal or subnormal level. Studies have been performed of the blood levels of thiouracil and its excretion in the urine. No serious complications from the drug have been encountered, but all patients receiving this drug should be followed carefully.—*D.A.M.*

WILLIAMS, R. H., E. EGANA, P. ROBINSON, S. P. ASPER, AND C. DUTOIT.

Alterations in biologic oxidation in thyrotoxicosis. 1. Thiamine metabolism. *Arch. Int. Med.* 72: 353. 1943.

The authors discuss the interrelationship of cellular oxidations and the functions of the thyroid gland. In the majority of a group of 40 unselected thyrotoxic subjects the levels of free thiamine and diphosphothiamine in the blood were below normal and that of pyruvic acid was elevated. In 5 of 7 of these patients the level of lactic acid was elevated. The thiamine deficiency was regarded as being due to the waste of this substance in the stools, sweat and urine, as well as to the excessive combustion of food. Thyrotoxic patients tend to excrete relatively large amounts of thiamine in the urine in spite of a deficiency of this substance in the blood. The excessive excretion of thiamine in the urine is due partially to the diuresis which these patients experience. No impairment of the phosphorylation of thiamine was demonstrable. During a period of 4 hours following the intravenous injection of 50 gm. of dextrose or 5 gm. of sodium pyruvate, the levels of pyruvic acid and lactic acid in the blood remained distinctly higher in thyrotoxic subjects than in normal persons. The response of the thiamine and diphosphothiamine in the blood varied, but these substances tended to remain at lower levels in thyrotoxic subjects than in normal ones. Since patients with hyperthyroidism tend to have a decreased amount of diffusible magnesium and diphosphothiamine in the blood, the experiments with dextrose or sodium pyruvate were repeated immediately after 5 mg. of diphosphothiamine had been given or the patient had been saturated with magnesium sulfate. These substances had essentially no effect on the blood sugar content but in some instances had a marked effect on the blood pyruvate and lactate. Administration of thiamine hydrochloride is of distinct advantage as an adjunctive measure in the treatment of thyrotoxicosis.—*I.B.*

WILLIAMS, R. D., AND E. C. KENDALL.

Influence of thiamine on induced hyperthyroidism. *Arch. Int. Med.* 72: 185. 1943.

Two physically healthy women, maintained continuously on a basal diet providing only 0.22 mg. of thiamine per 1,000 calories but adequate in all other respects, received large doses of desiccated thyroid gland (subject 1, 0.6 gm. per day; subject 2, 0.5 gm.) for 241 days. Besides the periods of preliminary and subsequent observation the study was divided into 3 periods: Thiamine hydrochloride was liberally provided during the first period, of 22 days; it was restricted to 0.45 mg. per day during the second period, of 136 days; it was provided in increasing amounts during the third period, of 81 days. The basal metabolic rate of each subject rose to approximately plus 25 per cent during the initial period of administration of thiamine and desiccated thyroid. It fell to minus 8 per cent and plus 11 per cent, respectively, during the period of restriction of thiamine, but rose to approximately plus 25 and plus 30 per cent, respectively, in the third period, when thiamine hydrochloride was again provided. Throughout the period of administration of desiccated thyroid, the concentrations of pyruvic acid and lactic acid in the blood after administration of dextrose were high, but they were higher during the period of restriction of thiamine. The conclusion appears justified that the thyroid hormone is less effective in promoting the metabolic activity of the organism in a state of thiamine deficiency. The results of this study may be interpreted as additional evidence that the function of the thyroid hormone is primarily to mobilize metabolites for oxidation by enzyme systems of the organism and only indirectly to increase the rate of oxidative processes. —*Authors' Summary and Conclusions.*—*I.B.*

WINKLER, A. W., J. CRISCUOLO, AND P. H. LAVIETES.

Quantitative relationship between basal metabolic rate and thyroid dosage in patients with true myxedema. *J. Clin. Invest.* 22: 531. 1943.

Twenty-eight patients with fully developed myxedema were observed under carefully supervised treatment for long periods of time. Changes in the clinical condition and in the basal metabolic rate were the criteria of improvement. Patients were never given more than enough desiccated thyroid substance to produce a satisfactory clinical course and establish a normal basal metabolic rate. Several facts seem to have been proven: 1) tolerance to thyroid substance does not develop in myxedematous patients; 2) the dosage necessary to maintain a satisfactory condition varies from patient to patient; but ranges between one and three grains daily; 3) a straight line relationship appears to exist between the dose of thyroid employed and the basal metabolic rate attained.—*T.H.McG.*

WINKLER, A. W., P. H. LAVIETES, C. L. ROBBINS, AND E. B. MAN.

Tolerance to oral thyroid and reaction to intravenous thyroxine in subjects without myxedema. *J. Clin. Invest.* 22: 535. 1943.

From a study of 36 non-myxedematous patients over periods ranging from months to years, the authors conclude that as much as six grains daily of desiccated thyroid substance may have no effect upon the basal metabolic rate or the pulse rate. Thyroxine intravenously administered produces a characteristic effect, although larger doses are necessary than those used in the treatment of myxedema. In view of the sharp contrast between the relative insensitivity of these patients and the reproducible and quantitative responses of patients with myxedema, it is suggested that the "non-myxedematous subject possesses the ability, wanting in the patient with myxedema, to inactivate thyroid substance and intravenous thyroxine."—*T.H.McG.*

WEYENETH, R., AND G. CHANAL.

Lymphadenoid thyroiditis (Hashimoto's goitre) in the Canton of Geneva. *Rev. Med. Suisse Rom.* 63: 681. 1943.

A detailed study of 8 cases is reported. The thyroids were characterized by massive adenoid infiltration of the parenchyma with formation of lymphatic follicles. The thyroid alveoli were markedly degenerated. In some areas dense sclerosis was seen. The underlying disorder was regarded not as an inflammatory process but as a metabolic derangement leading to primary epithelial degeneration. The condition appeared to be less serious than Hashimoto's goitre in that, instead of a 50% incidence of myxedema, only 2 of the cases presented that condition—and in light form. The condition was seen only in women and most commonly at the climacteric age. The problems of histopathology and etiology are discussed at length. As to treatment conservative surgery is advocated.—*R.G.H.*

WOLF, A.

The effective use of thyroid in periodic paralysis. *N. Y. State Jour. Med.* 43: 1951. 1943.

The author discusses the relationship of the endocrine system to periodic paralysis and reports the results of thyroid substance in seven patients with this disease. Treatment thus far has prevented the development of attacks for the past year and a half. The patients were all adults except one girl of fourteen years and were all related. The doses varied from one-half to one grain three times a day to larger doses just preceding an attack. The author discusses the role of the thyroid in this disease and concludes that thyroid substance neutralizes or prevents the onset of the seizure of periodic paralysis.

There is a familial variety of periodic paralysis without exophthalmic goiter which responds to thyroid and not to potassium, and a sporadic type of periodic paralysis which may or may not be accompanied by exophthalmic goiter which responds to potassium, to removal, or to irradiation of the thyroid gland and is aggravated by thyroid substance.

If the seizures represent thyroid failure, there may be compensatory anterior pituitary oversecretion which produces temporary exophthalmos and possibly even generalized muscle weakness. It is possible that the seizure of periodic paralysis may be due to adrenal insufficiency. On the other hand, adrenalin may exercise paralytic effect only in cases where there has developed a degree of hyperthyroidism.—*M.B.G.*